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**APPLICATION FOR  
PATENT TERM EXTENSION  
UNDER 35 U.S.C. § 156**

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Application Number	08/696,987
First Named Inventor	Sandra Doreen Anderson
Filing Date	February 23, 1995
Confirmation No.	9268
Patent No.	5,817,028
Issue Date	October 6, 1998
Group Art Unit	3736
Examiner Name	HUANG, STEPHEN D.
Attorney Docket No.	RICE-126
Title:	<i>"METHOD AND DEVICE FOR THE PROVOCATION OF AIR PASSAGE NARROWING AND/OR THE INDUCTION OF SPUTUM"</i>

Dear Sir:

Pursuant to 35 U.S.C. § 156 and 37 C.F.R. §§ 1.710-1.791, Pharmaxis Ltd. ("Applicant"), through its undersigned duly authorized attorney/agent, hereby requests an extension of the patent term of U.S. Patent No. 5,817,028 ("the '028 patent").

**PATENT TERM EXTENSION APPLICATION UNDER 35 U.S.C. § 156**

Applicant, Pharmaxis Ltd., is the licensee of Application No. 08/696,987, filed on February 23, 1995, which later issued as U.S. Patent No. 5,817,028 on October 6, 1998. Documentary evidence of the assignment from the original owner, Sandra Doreen Anderson, to Central Sydney Area Health Service (“CSAHS”) is attached as Exhibit A. On October 10, 2001, CSAHS licensed the rights to the ‘028 patent to Praxis Pharmaceuticals Australia Pty Ltd. (“Praxis”). (See Exhibit B). Subsequently, Praxis changed its name from “Praxis Pharmaceuticals Australia Pty Ltd.” to “Pharmaxis Pty Ltd.”, and then from “Pharmaxis Pty Ltd.” to “Pharmaxis Ltd.” (“Pharmaxis”; See Exhibit C).

In addition, in 2004, Central Sydney Area Health Service was amalgamated from “Central Sydney Area Health Service” to “Sydney South West Area Health Service” by virtue of Health Services (Amalgamation of Area Health Services) Order 2004 under the Health Services Act 1997. (See Exhibit D). Additional information regarding amalgamations can be found in New South Wales Consolidated Acts: Health Services Act 1997 – Schedule 4. (See Exhibit E). In particular, Part 2, Division 3 of the Act indicates that “the assets of the transferor vest in the transferee by virtue of this clause and without the need for any further conveyance, transfer, assignment or assurance”. (See Exhibit E).

Additionally, Applicant submits concurrently with this filing a “Power of Attorney and Correspondence Address Indication Form” (PTO/SB/81) along with the supporting “Statement under 37 C.F.R. § 3.73(b)” form (PTO/SB/96).

This application for patent term extension is based on the U.S. regulatory approval of Aridol™ indicated for the assessment of bronchial hyperresponsiveness in patients 6 years of age or older who do not have clinically apparent asthma. Applicant is the holder of marketing approval for Aridol™.

The expiration date of the ‘028 patent is October 6, 2015. The ‘028 patent includes claims directed to a method for attempting to provoke airway narrowing in a subject. The method includes: (a) causing the subject to inhale into subject’s airways an effective amount of a substance capable of increasing the osmolarity of airway surface liquid in the subject, which substance is in the form of a dry dispersible powder, other than a dry powder dissolved in a

liquid, containing an effective proportion of particles of a respirable size; and (b) measuring in the subject a parameter indicative of the resistance to air flow of the subject's airway. The method of using Aridol™ falls within the scope of these claims. The extension of patent term requested for the '028 patent is until June 16, 2019, which includes 1,349 days of patent term extension.

The date of the New Drug Application approval for Aridol™ (dry mannitol inhalation powder) was October 5, 2010. Applicant believes this is the first permitted commercial marketing or use of this product in the United States. This application is being made within the sixty day statutory period provided in 35 U.S.C. § 156(d).

Applicant, through its duly authorized attorney, hereby submits this application for patent term extension under 35 U.S.C. § 156 by providing the following information required by the statute and in accordance with the provisions of 37 C.F.R. § 1.740. For the convenience of the USPTO, the information in this application is presented in the order set forth in 37 C.F.R. § 1.740.

**1. A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAME, PHYSICAL STRUCTURE OR CHARACTERISTICS (37 C.F.R. § 1.740(a)(1)).**

The approved product, Aridol™ ("the Product"), is a dry inhalation powder of mannitol. Dry inhalation powder mannitol is described as follows.

Compendial names:

European Pharmacopoeia (Ph. Eur.): Mannitol

United States Pharmacopeia (USP): Mannitol

British Pharmacopoeia (BP): Mannitol

Japanese Pharmacopoeia (JP): D-Mannitol

Chemical Name:

hexane-1,2,3,4,5,6-hexol

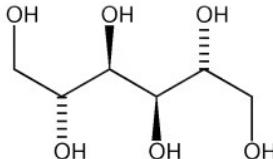
Other non-proprietary names:

Cordycepic acid, E421, manita; manna sugar, mannite, D-mannitol, mannitolum, mannogen

CAS Registry Number:

69-65-8

Structural Formula:



Empirical Formula:

C<sub>6</sub>H<sub>14</sub>O<sub>6</sub>

Molecular Weight:

182.17

Description:

Mannitol is described in monographs of the USP, Ph. Eur. and BP. The drug substance is a white or almost white, crystalline powder or free-flowing granules. Mannitol shows polymorphism.

Solubility:

Mannitol is freely soluble in water, and very slightly soluble in alcohol.

Melting Point:

164°C to 169°C

Morphic forms:

There are three morphic forms of mannitol commonly denoted as  $\alpha$ ,  $\beta$ ,  $\delta$ -mannitol

Dissociation constant:

pKa = 13.5 at 18 °C

Hygroscopicity:

Mannitol resists moisture sorption, even at high relative humidity

### **Manufacturing Process**

During manufacture of dry inhalation powder mannitol for Aridol™, a spray drying procedure is used, followed by filling of the spray dried mannitol inhalation powder into gelatin capsules.

The spray-drying procedure was developed to produce a respirable mannitol powder suitable for inhalation and diagnosis of asthma. By passing a solution of known concentration of mannitol through a process of liquid atomization, the solution is converted to a fine mist followed by rapid hot air drying. This process results in the production of particles that are of respirable size and spherical in shape that make them disperse well when aerosolized.

As described in more detail in section 4 below, spray-dried inhalation powder mannitol has a median particle size of 2.9  $\mu\text{m}$ . In addition, the spray-drying procedure produces a particle

size distribution of:  $d_{10}$  of  $1.9 \pm 0.3 \mu\text{m}$ ;  $d_{50}$  of  $2.9 \pm 0.2 \mu\text{m}$ ;  $d_{90}$  of  $4.6 \pm 0.6 \mu\text{m}$ . Spray-dried inhalation powder mannitol for Aridol™ has defined physical characteristics and particle size distribution in the range that is considered respirable. In addition, spray-dried inhalation powder mannitol has a composition that contains a mixture of three mannitol polymorphs, including >90%  $\beta$ -mannitol, <10%  $\alpha$ -mannitol and <1%  $\delta$ -mannitol.

Sub-batches of spray-dried inhalation powder mannitol are produced. A larger batch is then prepared by pooling and blending a number of sub-batches. The resulting batch of spray-dried inhalation powder mannitol is used to prepare 5 mg, 10 mg, 20 mg and 40 mg Aridol™ capsules. The capsules are packed into double aluminum blisters. The filled blisters are placed into a carton with instruction and doctor/patient information leaflet and the dry powder inhalation device.

No excipients are included in the contents of the capsules (e.g., the 0 mg capsules are empty). Water for injection is used during manufacture but removed during the manufacturing process.

#### **Aridol™ Bronchial Challenge Test**

The Aridol™ (dry mannitol inhalation powder) bronchial challenge test (BCT) is a complete diagnostic test kit containing the required capsules of dry inhalation powder mannitol and a disposable, proprietary dry powder inhaler to perform one indirect BCT for one patient. The BCT challenge test is administered by a health care professional. The following nine doses of dry inhalation powder mannitol are inhaled sequentially by the patient (0, 5, 10, 20, 40, 80, 160, 160, and 160 mg). The dry inhalation powder mannitol is contained in hard gelatin capsules and administered through a single dose dry powder inhaler. The capsules for inhalation contain 0, 5, 10, 20, and 40 mg of dry inhalation powder mannitol. Therefore, doses of 80 and 160 mg are delivered by rapidly inhaling the contents of two and four 40 mg capsules, respectively. Spirometry is performed immediately after each serial inhalation. Dosing is stopped (i.e., the test is positive) when either forced expiratory volume measured in one second (FEV<sub>1</sub>) decreases 15% or more from baseline or decreases  $\geq 10\%$  from the value obtained following the immediate previous dose. Testing is negative if all doses of mannitol are inhaled (635 mg total) without decreases in overall FEV<sub>1</sub>  $\geq 15\%$  or a decrease  $\geq 10\%$  from the value obtained following the

immediate previous dose. At baseline and following each dose, a measure of FEV<sub>1</sub> is made. The test result expressed is a PD<sub>15</sub>.

**2. A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED (37 C.F.R. § 1.740(a)(2)).**

The regulatory review for Aridol™ (dry inhalation powder mannitol) occurred under Section 505 of the Federal Food, Drug, and Cosmetic Act (“FFDCA”), codified in 21 U.S.C. § 355.

**3. AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED (37 C.F.R. § 1.740(a)(3)).**

The Food and Drug Administration (“FDA”) approved Aridol™ (dry inhalation powder mannitol) for commercial marketing or use on October 5, 2010. A copy of the approval letter is found as Exhibit F.

**4. AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FEDERAL FOOD, DRUG, AND COSMETIC ACT, THE PUBLIC HEALTH SERVICE ACT, OR THE VIRUS-SERUM-TOXIN ACT, OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER ALONE OR IN COMBINATION WITH OTHER ACTIVE INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED, AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED (37 C.F.R. § 1.740(a)(4)).**

Aqueous solutions of mannitol have been previously approved under Section 505 of the FFDCA. These prior approvals include New Drug Application (“NDA”) numbers 013684 (June 8, 1964), 014738 (July 30, 1964), 016080 (October 8, 1965), 016269 (December 22, 1967), 019603 (January 8, 1987), and 020006 (July 26, 1993) for aqueous solutions of mannitol indicated for the promotion of diuresis in the prevention and/or treatment of the oliguric phase of acute renal failure before irreversible renal failure becomes established, the reduction of intracranial pressure and treatment of cerebral edema by reducing brain mass, the reduction of

elevated intraocular pressure when the pressure cannot be lowered by other means, and the promotion the urinary excretion of toxic substances. In addition, injectable aqueous solutions of mannitol have been approved under Section 505 of the FFDCA for the above indications for Abbreviated New Drug Application (ANDA) numbers 080677 (August 11, 1972) and 083051 (August 29, 1975). Aqueous solutions of mannitol have also been previously approved under Section 505 of the FFDCA for use as a urological irrigation fluid for transurethral prostatic resection and other transurethral surgical procedures. These prior approvals include NDA numbers 017636 (June 21, 1976), 016772 (February 10, 1978), and 018316 (February 22, 1980). In addition, aqueous irrigation solutions of mannitol have been previously approved for use as a urological irrigation fluid for transurethral prostatic resection and other transurethral surgical procedures for ANDA number 080224 (August 20, 1971). Mannitol has also been included in previously approved drugs as an inactive excipient, such as in NDA number 021868 (January 27, 2006), which was approved under Section 505 of the FFDCA for the regulation of glucose metabolism and includes inhaled insulin as the active ingredient.

The approved product, Aridol™ ("the Product"), is a dry inhalation powder of mannitol. Dry inhalation powder mannitol, the only active ingredient in Aridol™, is a sugar alcohol indicated for the assessment of bronchial hyperresponsiveness in patients 6 years of age or older who do not have clinically apparent asthma.

Applicant believes that dry inhalation powder of mannitol as an active ingredient has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act.

The impact of the spray drying procedure on mannitol has been investigated as a part of the process development and product characterization.

Operating parameters for the spray-drying process have been optimized and validated to deliver a drug product with the correct particle size distribution, moisture content and shape. The properties of dry inhalation powder mannitol that may be altered by the spray drying process are the aerodynamic particle size distribution, polymorphic composition and water content.

#### *Particle Size*

The particle size distribution of spray-dried mannitol was determined by laser diffraction during the manufacturing process development. The median particle size was 2.9 µm. The spray-drying procedure produces a particle size distribution of:  $d_{10}$  of  $1.9 \pm 0.3$  µm;  $d_{50}$  of

$2.9 \pm 0.2 \mu\text{m}$ ;  $d_{90}$  of  $4.6 \pm 0.6 \mu\text{m}$ . In contrast to earlier approved aqueous solutions of mannitol, which include mannitol dissolved in water, spray-dried mannitol has defined physical characteristics and particle size distribution in the range that is considered respirable.

The particle size distribution by laser diffraction is currently measured as an in-process control. The aerodynamic particle size distribution (APSD) is measured as a batch release test and monitored in the stability program. APSD is examined as per the current USP <601>, by use of Apparatus 3 (ACI).

#### *Crystal Structure*

Examination of mannitol particles before and after spray drying has shown that the particles change from an irregular crystalline to spherical shape. This change affects the aerodynamic properties of the dry inhalation powder mannitol particles.

The possibility of transformations during spray-drying has been investigated using various technologies (e.g., scanning electron microscopy, X-ray diffraction). SEM and XRD results indicate that the spray-dried mannitol contained no amorphous material. Spray-dried inhalation powder mannitol was found to contain a mixture of three mannitol polymorphs,  $\alpha$ ,  $\beta$  and  $\delta$ . Spray-dried inhalation powder mannitol for Aridol™ has a composition of >90%  $\beta$ -mannitol, <10%  $\alpha$ -mannitol and <1%  $\delta$ -mannitol.

Analysis of spray-dried mannitol produced under the validated operating conditions showed that all samples were classified as typical production material at batch release and over the proposed shelf life.

In summary, dry inhalation powder mannitol for Aridol™ has defined physical characteristics and particle size distribution in the range that is considered respirable. Spray-drying forms dry inhalation powder mannitol particles that have a spherical shape, rather than an irregular crystalline shape, which affects the aerodynamic properties of the dry inhalation powder mannitol particles. For instance, dry inhalation powder mannitol has a median particle size of  $2.9 \mu\text{m}$  with a particle size distribution of:  $d_{10}$  of  $1.9 \pm 0.3 \mu\text{m}$ ;  $d_{50}$  of  $2.9 \pm 0.2 \mu\text{m}$ ;  $d_{90}$  of  $4.6 \pm 0.6 \mu\text{m}$ , which allows for respiration of dry inhalation powder mannitol into the lungs during the bronchial challenge test. These properties are not found in the previously approved aqueous solutions of mannitol.

**5. A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED  
WITHIN THE SIXTY DAY PERIOD PERMITTED FOR SUBMISSION  
PURSUANT TO § 1.720(f) AND AN IDENTIFICATION OF THE DATE OF  
THE LAST DAY ON WHICH THE APPLICATION COULD BE  
SUBMITTED (37 C.F.R. § 1.740(a)(5)).**

This application is being submitted within the sixty-day period following October 5, 2010, the NDA approval date, as provided in 37 C.F.R. § 1.720(f). The sixty-day period following October 5, 2010 ends on December 4, 2010, which is a Saturday. The last day on which the application could be submitted that is not a Saturday, Sunday or holiday is December 6, 2010. Therefore, this application is being submitted within the sixty-day statutory period provided in 35 U.S.C. § 156(d).

**6. A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN  
EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR,  
THE PATENT NUMBER, THE DATE OF ISSUE, AND THE DATE OF  
EXPIRATION (37 C.F.R. § 1.740(a)(6)).**

Inventor: Sandra Doreen Anderson

Patent No. 5,817,028

Date of Issue: October 6, 1998

Date of Expiration: October 6, 2015

**7. A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING  
SOUGHT, INCLUDING THE ENTIRE SPECIFICATION (INCLUDING  
CLAIMS) AND DRAWINGS (37 C.F.R. § 1.740(a)(7)).**

A copy of the '028 patent for which extension is being sought, including the entire specification (including claims), is found as Exhibit G.

**8. A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION,  
RECEIPT OF MAINTENANCE FEE PAYMENT, OR REEXAMINATION  
CERTIFICATE ISSUED IN THE PATENT (37 C.F.R. § 1.740(a)(8)).**

A copy of a Certificate of Correction for the '028 patent is found as Exhibit H.

The first maintenance fee required under 37 C.F.R. § 1.362(d)(1) for U.S. Patent No. 5,817,028 was timely paid on March 21, 2002. The first maintenance fee was paid for U.S. Patent No. 5,817,028 as a large entity as shown by the relevant USPTO Maintenance Fee Statement. (See Exhibit I). The second maintenance fee required under 37 C.F.R. § 1.362(d)(2)

for U.S. Patent No. 5,817,028 was timely paid on March 13, 2006. The second maintenance fee was paid for U.S. Patent No. 5,817,028 as a large entity as shown by the relevant USPTO Maintenance Fee Statement. (See Exhibit J). The third maintenance fee required under 37 C.F.R. § 1.362(d)(3) for U.S. Patent No. 5,817,028 was timely paid on March 31, 2010. The third maintenance fee was paid for U.S. Patent No. 5,817,028 as a large entity as shown by the relevant USPTO Maintenance Fee Statement. (See Exhibit K).

**9. A STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT, OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH AT LEAST ONE SUCH PATENT CLAIM READS ON THE METHOD OF USING THE APPROVED PRODUCT (37 C.F.R. § 1.740(a)(9)).**

The method of using the approved product, Aridol™, falls within the scope of certain claims of the '028 patent. The following chart demonstrates the manner in which at least one claim of the '028 patent reads on the method of using the approved product, Aridol™, as required by 37 C.F.R. § 1.740(a)(9).

Applicable Claims of the '028 Patent	Manner in which at Least One Independent Claim of the '028 Patent Reads on the Method of Using the Approved Product, Aridol™
<p>1. A method for attempting to provoke airway narrowing in a subject comprising the steps of</p> <p>(a) causing the subject to inhale into subject's airways an effective amount of a substance capable of increasing the osmolarity of airway surface liquid in the subject, which substance is in the form of a dry dispersible powder, other than a dry powder dissolved in a liquid, containing an effective proportion of particles of a respirable size, and</p> <p>(b) measuring in the subject a parameter indicative of the resistance to air flow of the subject's airway.</p>	<p>Aridol™ (dry inhalation powder mannitol) is administered as part of a bronchial challenge test (BCT).</p> <p>During the test, a patient inhales dry inhalation powder mannitol in sequential doses of 0, 5, 10, 20, 40, 80, 160, 160, and 160 mg.</p> <p>As described above, the dry inhalation powder mannitol is produced by a spray-drying process. The spray-drying procedure results in a particle size distribution of: <math>d_{10}</math> of <math>1.9 \pm 0.3 \mu\text{m}</math>; <math>d_{50}</math> of <math>2.9 \pm 0.2 \mu\text{m}</math>; and <math>d_{90}</math> of <math>4.6 \pm 0.6 \mu\text{m}</math> for the dry inhalation powder mannitol.</p>

	Spirometry is performed immediately after each serial inhalation. Dosing is continued until a positive result is achieved (e.g., either a $\geq 15\%$ fall from baseline in FEV <sub>1</sub> or a 10% fall from the previous dose) or until the maximum cumulative dose of 635 mg has been administered without meeting either criterion (i.e., a negative test).
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At least one independent claim (e.g., independent claim 1), and at least one dependent claim thereof (e.g., dependent claims 2-11) of the '028 patent read on the method of using the approved product, Aridol™;

1. A method for attempting to provoke airway narrowing in a subject comprising the steps of (a) causing the subject to inhale into subject's airways an effective amount of a substance capable of increasing the osmolarity of airway surface liquid in the subject, which substance is in the form of a dry dispersable powder, other than a dry powder dissolved in a liquid, containing an effective proportion of particles of a respirable size, and (b) measuring in the subject a parameter indicative of the resistance to air flow of the subject's airway.
2. A method as claimed in claim 1 in which the subject is caused to inhale the substance into the airways of a lung.
3. A method as claimed in claim 1 in which the subject is caused to inhale the substance into a nasal airway.
4. A method as claimed in claim 1 in which the substance is selected from the group comprising mineral salts, sugars and sugar alcohols.
5. A method as claimed in claim 4 in which the substance is selected from the group comprising salts of sodium or potassium, hexose and pentose sugars and their corresponding sugar alcohols.
6. A method as claimed in claim 5 in which the substance is selected from the group comprising sodium chloride, potassium chloride, mannitol and dextrose.
7. A method as claimed in claim 1 in which an effective quantity of the dry particles have a maximum dimension of seven microns.

8. A method as claimed in claim 1 in which the proportion of the particles having a respirable size is at least 10% by weight of the substance, preferably at least 25%, more preferably at least 40% and most preferably at least 50%.
9. A method as claimed in claim 1 in which the parameter indicative of airway narrowing that is measured comprises measuring a reduction in forced expiratory volume in one second.
10. A method as claimed in claim 1 in which the substance is packaged in a rupturable hard capsule.
11. A method as claimed in claim 10 in which the capsule contains from 1 to 100 mg of the substance, preferably 5 to 40 mg.

If the USPTO would like additional information about the above listed claims and how any one of the claims reads on the method of using the approved product, Aridol™, Applicant will provide such information upon request.

10. A STATEMENT BEGINNING ON A NEW PAGE OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. § 156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD, PARTICULARLY FOR A PATENT CLAIMING A HUMAN DRUG, ANTIBIOTIC, OR HUMAN BIOLOGICAL PRODUCT, THE EFFECTIVE DATE OF THE INVESTIGATIONAL NEW DRUG (IND) APPLICATION AND THE IND NUMBER; THE DATE ON WHICH A NEW DRUG APPLICATION (NDA) OR A PRODUCT LICENSE APPLICATION (PLA) WAS INITIALLY SUBMITTED AND THE NDA OR PLA NUMBER; AND THE DATE ON WHICH THE NDA WAS APPROVED OR THE PRODUCT LICENSE ISSUED (37 C.F.R. § 1.740(a)(10)).

NDA number 022368 was submitted and approved for Aridol™ (dry inhalation powder mannitol). The relevant dates are as follows:

Date on which Pre-IND Meeting was held	July 19, 2004
Date on which original IND number 70,277 was submitted	November 19, 2004
Date on which original IND number 70,277 became effective	December 22, 2004
Date on which original NDA number 022368 was submitted	February 27, 2009
Date on which Action Letter was issued	December 23, 2009
Date on which NDA number 022368 was resubmitted	April 7, 2010
Date on which original NDA number 022368 was approved by the FDA	October 5, 2010

The '028 patent claims a method of using the approved product, Aridol™. A Pre-IND meeting (IND number 70,277) was held on July 19, 2004. Clinical Study DPM-A-301 ("Study 301"), the pivotal study used for approval in Australia and other countries, was discussed. Applicant obtained confirmation from the FDA that Study 301 could be used to provide supportive safety data for the NDA filing. A single pivotal study was proposed to evaluate the efficacy and safety of the dry inhalation powder mannitol bronchial challenge test for the proposed indication. On November 19, 2004, IND number 70,277 was opened in which a protocol for a phase 3 study, DPM-A-305 ("Study 305"), was submitted. (See Exhibit L). The date of receipt of IND number 70,277 by the FDA was November 22, 2004. (See Exhibit M). IND number 70,277 became effective on December 22, 2004 (i.e., 30 days after IND number

70,277 was received). This establishes the beginning of the “regulatory review period” under 35 U.S.C. § 156(g)(1)(B)(i) as December 22, 2004, the effective date of an investigational new drug exemption.

On February 27, 2009, Applicant submitted an original New Drug Application (“NDA”) for Aridol™. (See Exhibit N). The NDA was assigned number 022368 by the FDA. (See Exhibit O). The regulatory review for Aridol™ occurred under Section 505 of the Federal Food, Drug, and Cosmetic Act (“FFDCA”). This establishes February 27, 2009 as “the date an application was initially submitted” under 35 U.S.C. § 156(g)(1)(B)(i). The submission of the original NDA for Aridol™ also establishes February 27, 2009 as “the date the application was initially submitted for the approved product” under 35 U.S.C. § 156(g)(1)(B)(ii).

On December 23, 2009, the FDA issued a Complete Response Letter. (See Exhibit P). A Complete Response Resubmission was submitted by Applicant on April 7, 2010. (See Exhibit Q). On October 5, 2010, the FDA approved NDA number 022368 for dry inhalation powder mannitol, the active ingredient in Aridol™, indicated for the assessment of bronchial hyperresponsiveness in patients 6 years of age or older who do not have clinically apparent asthma. (See Exhibit F). This establishes the end of the “regulatory review period” under 35 U.S.C. § 156(g)(1)(B)(ii) as October 5, 2010.

**11. A BRIEF DESCRIPTION BEGINNING ON A NEW PAGE OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY THE MARKETING APPLICANT DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES (37 C.F.R. § 1.740(a)(11)).**

During the regulatory review period, Applicant was actively involved in obtaining FDA approval for the approved product, Aridol™.

On February 27, 2009, Applicant submitted an original NDA number 022368 for Aridol™ indicated for the assessment of bronchial hyperresponsiveness in patients 6 years of age or older who do not have clinically apparent asthma under Section 505 of the FFDCA. (See Exhibit N).

In a letter dated May 12, 2009, to Pharmaxis, from the FDA, NDA number 022368 was determined to be sufficiently complete to permit substantive review. (See Exhibit R).

In a Complete Response Letter dated December 23, 2009, to Pharmaxis, from the FDA, Pharmaxis was notified that the FDA had completed the review of NDA number 022368 and determined that the application could not be approved in its current form. (See Exhibit P). The FDA indicated possible recommendations to address the issues.

On April 7, 2010, Applicant responded to the Complete Response Letter by submitting a Complete Response Resubmission for NDA number 022368. (See Exhibit Q). In the Complete Response Resubmission, Applicant addressed the remaining issues for the NDA final approval.

Following submission of the Complete Response Resubmission, NDA number 022368 was granted approval for commercial distribution on October 5, 2010. (See Exhibit F).

In summary, the regulatory review period began on December 22, 2004, when the original IND number 70,277 became effective. (See Exhibits L and M). During the period from December 22, 2004 through February 27, 2009, Applicant conducted clinical trials and acted with due diligence during the phase of the regulatory review period under 35 U.S.C. § 156(g)(1)(B)(i).

On February 27, 2009, Applicant submitted original NDA number 022368 for Aridol™. (See Exhibit N). From the time NDA number 022368 was received by the FDA on February 27, 2009 to October 5, 2010, when Applicant received regulatory approval for NDA number 022368, Applicant continued to work in close consultation with the FDA by answering questions, generating requested data, and supplying requested information regarding the clinical studies and

data on Aridol™. Applicant acted with due diligence under NDA number 022368 during the phase of the regulatory review period under 35 U.S.C. § 156(g)(1)(B)(ii), which ended when NDA number 022368 was approved by the FDA.

Exhibit S identifies submissions and communications between Applicant and the FDA concerning IND number 70,277 and NDA number 022368, briefly describes significant and other activities by Applicant during the regulatory review phases under 35 U.S.C.

§ 156(g)(1)(B)(i) and 35 U.S.C. § 156(g)(1)(B)(ii), and confirms that Applicant acted with due diligence during these phases of the regulatory review period.

Applicant does not believe that copies of any further submissions or communications identified during the regulatory review period are required to be submitted pursuant to 37 C.F.R. § 1.765. Copies of any or all of the submissions and communications required to support the above brief description will be provided to the USPTO upon request.

Applicant reserves the right to present additional information in support of the conclusion that it acted with due diligence during the regulatory review period. See, e.g., 21 C.F.R. § 60.32.

**12. A STATEMENT BEGINNING ON A NEW PAGE THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR THE EXTENSION AND A STATEMENT AS TO THE LENGTH OF EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED (37 C.F.R. § 1.740(a)(12)).**

**a. Statement of Eligibility**

Applicant believes that it is entitled to a patent term extension for the '028 patent under 35 U.S.C. § 156 because it satisfies all of the requirements for such extension as follows:

**1. 35 U.S.C. § 156(a), 37 C.F.R. § 1.720**

The claims of U.S. Patent No. 5,817,028 encompass the approved product, Aridol™.

**2. 35 U.S.C. § 156(a)(1)**

Pursuant to 35 U.S.C. § 154(c)(1), as amended (effective June 8, 1995) by the Uruguay Round Agreements Act, Pub. L. 103-465, 108 Stat. 4809 (1994), and 35 U.S.C. § 156, the term of the '028 patent currently expires on October 6, 2015. Therefore, the term of the '028 patent will not have expired before submission of this application.

**3. 35 U.S.C. § 156(a)(2)**

The term of the '028 patent has never been extended under 35 U.S.C. § 156(e)(1).

**4. 35 U.S.C. § 156(a)(3)**

This application for patent term extension is submitted by an attorney for the licensee of the owner of record in accordance with the requirements of 35 U.S.C. § 156(d)(1)-(4) and the rules of the USPTO.

**5. 35 U.S.C. § 156(a)(4)**

As shown by the October 5, 2010 letter from the FDA to Applicant (See Exhibit F), the approved product, Aridol™, was subject to a regulatory review period under Section 505 of the FFDCA before its commercial marketing or use.

**6. 35 U.S.C. § 156(a)(5)(A)**

Applicant believes that the commercial marketing or use of the approved product, Aridol™ (dry inhalation powder mannitol as an active ingredient), is the first permitted commercial marketing or use of the product under Section 505 of the FFDCA.

As described in section 4 above, spray-dried inhalation powder mannitol has a median particle size of 2.9 µm. In addition, the spray-drying procedure produces a particle size distribution of:  $d_{10}$  of  $1.9 \pm 0.3$  µm;  $d_{50}$  of  $2.9 \pm 0.2$  µm;  $d_{90}$  of  $4.6 \pm 0.6$  µm. Although mannitol has been previously approved as aqueous injectable solutions and aqueous irrigation solutions for

various indications, dry inhalation powder mannitol as an active ingredient, as contained in Aridol™, has never been previously approved for any indication.

As discussed above, dry inhalation powder mannitol for Aridol™ has defined physical characteristics and particle size distribution in the range that is considered respirable. Spray-drying forms dry inhalation powder mannitol particles that have a spherical shape, rather than an irregular crystalline shape, which affects the aerodynamic properties of the dry inhalation powder mannitol particles. For instance, dry inhalation powder mannitol has a median particle size of 2.9 µm with a particle size distribution of: d<sub>10</sub> of 1.9 ± 0.3 µm; d<sub>50</sub> of 2.9 ± 0.2 µm; d<sub>90</sub> of 4.6 ± 0.6 µm, which allows for respiration of dry inhalation powder mannitol into the lungs during the bronchial challenge test. These properties are not found in the previously approved aqueous solutions of mannitol.

#### **7. 35 U.S.C. § 156(c)(4)**

No other patent has been extended under 35 U.S.C. § 156(e)(1) for the same regulatory review period for the approved product, Aridol™.

#### **b. Statement of Length of Extension and Determination of Such Extension**

Applicant believes that the period of extension applicable to the '028 patent is 1,349 days or to June 16, 2019, based on the following chronology:

<b>Patent Extension Calculation</b>	<b>Calculations</b>
Date on which original IND number 70,277 became effective	December 22, 2004
Date on which original NDA number 022368 was submitted	February 27, 2009
Date on which original NDA number 022368 was approved by the FDA	October 5, 2010
Effective patent filing date	February 23, 1995
U.S. Patent No. 5,817,028 issue date	October 6, 1998
17 years from issue date	October 6, 2015
20 years from effective patent filing date	February 23, 2015
Greater of 17 years from issue or 20 years from filing	October 6, 2015
Start date of regulatory review period	December 22, 2004
35 U.S.C. § 156(g)(1)(B)(i) review period (days)	1,528
½ of 35 U.S.C. § 156(g)(1)(B)(i) review period (days)	764

35 U.S.C. § 156(g)(1)(B)(ii) review period (days)	585
Total regulatory review period (days)	2,113
§ 156(g)(1)(B)(ii) period + ½ § 156(g)(1)(B)(i) period (days)	1,349
Statutory extension period in days	1,349

The current term of the '028 patent, which expires on October 6, 2015, should be extended by 1,349 days, or to June 16, 2019. This period of extension was determined on the following basis.

As set forth in 35 U.S.C. § 156(g)(1), the regulatory review period for the new drug Aridol™ equals the sum of the following two time periods: (i) the period of time beginning on the date original IND number 70,277 became effective on December 22, 2004, and ending on the date of submission of original NDA number 022368 on February 27, 2009, a period of 1,528 days; and (ii) the period of time beginning on the date of submission of original NDA number 022368 on February 27, 2009, and ending with the approval of original NDA number 022368 on October 5, 2010, a period of 585 days. The two periods added together equals 2,113 days.

Section 156(c)(2) requires the period calculated under 35 U.S.C. § 156(g)(1)(B)(i) (i.e., the period of time beginning on the date original IND number 70,277 became effective and ending on the date of submission of original NDA number 022368) to be reduced by one-half of the 1,528 day period, resulting in a period of 764 days.

From the above calculations, an extension of 1,349 days results, i.e., one-half the period under 35 U.S.C. § 156(g)(1)(B)(i) (764 days) plus the period under 35 U.S.C. § 156(g)(1)(B)(ii) (585 days).

This extension is subject to two potential limitations under 35 U.S.C. § 156. First, under 35 U.S.C. § 156(g)(6)(A), a maximum extension of five years is permitted. Since the calculated extension of 1,349 days is less than five years (i.e., 1,826 days), the patent term extension of 1,349 days is not limited by 35 U.S.C. § 156(g)(6)(A). Second, under 35 U.S.C. § 156(c)(3), if the period remaining in the term of the patent after the date of FDA approval (i.e., October 5, 2010), when added to the extension period calculated above would exceed 14 years, the period of extension is to be limited so that the total extension does not exceed 14 years. Here, a combination of the remaining term of the patent until October 6, 2015 and 1,349 days of

extension (i.e., until June 16, 2019) is less than the 14 year limit. As a result, the patent term extension of 1,349 days is not reduced under 35 U.S.C. § 156(c)(3).

Accordingly, the '028 patent is eligible for an extension of 1,349 days, from October 6, 2015 to June 16, 2019.

**13. A STATEMENT THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE AND THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT (SEE 37 C.F.R. § 1.765) (37 C.F.R. § 1.740(a)(13)).**

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought. In furtherance of that duty, Applicant herein explains that the '028 patent is eligible for patent term extension under 35 U.S.C. § 156.

**14. PRESCRIBED FEE (37 C.F.R. § 1.740(a)(14)).**

The government filing fee of \$1,120 required under 37 C.F.R. § 1.20(j) is charged herewith by credit card electronically. Please charge any additional fees or credit any overpayment in connection with the present application to Deposit Account No. 50-0815.

**15. CORRESPONDENCE INFORMATION (37 C.F.R. § 1.740(a)(15)).**

Inquiries and correspondence relating to the present application for patent term extension should be directed to:

Rudy J. Ng  
BOZICEVIC, FIELD & FRANCIS LLP  
1900 University Ave., Suite 200  
East Palo Alto, CA 94303  
Telephone: (650) 327-3400  
Fax: (650) 327-3231

#### **16. DECLARATION OF ATTORNEY/AGENT**

A patent term extension under 35 U.S.C. § 156 is being sought for U.S. Patent No. 5,817,028.

The undersigned representative of the Applicant avers that the undersigned is a patent attorney authorized to practice before the Patent and Trademark Office and who has general authority from the owner to act on behalf of the owner in patent matters, has reviewed and understands the contents of the application being submitted pursuant to this section, believes the patent is subject to extension pursuant to 37 C.F.R. § 1.710, believes an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations, believes the patent for which extension is being sought meets the conditions for extension of the term of the patent as set forth in 37 C.F.R. § 1.720. The undersigned further declares that all statements made herein of the undersigned's own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the requested extension.

Date: December 3, 2010

Respectfully submitted,  
BOZICEVIC, FIELD & FRANCIS LLP

/Rudy J. Ng, Reg. No. 56,741/  
Rudy J. Ng  
(Registration No. 56,741)

/Carol L. Francis, Reg. No. 36,513/  
Carol L. Francis, Ph.D.  
(Registration No. 36,513)

/Edward J. Baba, Reg. No. 52,581/  
Edward J. Baba  
(Registration No. 52,581)

Enclosures

BOZICEVIC, FIELD & FRANCIS LLP  
1900 University Ave., Suite 200  
East Palo Alto, CA 94303  
Telephone: (650) 327-3400  
Fax: (650) 327-3231

**TABLE OF EXHIBITS**

- 
- A Assignment for U.S. Patent No. 5,817,028
  - B Redacted Copy of Patent License Agreement for U.S. Patent No. 5,817,028
  - C Name Change Document
  - D Health Services (Amalgamation of Area Health Services) Order 2004
  - E New South Wales Consolidated Acts: Health Services Act 1997 – Schedule 4
  - F FDA Approval Letter for NDA No. 022368
  - G U.S. Patent No. 5,817,028
  - H Certificate of Correction for U.S. Patent No. 5,817,028
  - I First Maintenance Fee Statement (U.S. Patent No. 5,817,028)
  - J Second Maintenance Fee Statement (U.S. Patent No. 5,817,028)
  - K Third Maintenance Fee Statement (U.S. Patent No. 5,817,028)
  - L Cover Letter for Submission of Original IND Number 70,277
  - M FDA Acknowledgement Letter for IND Number 70,277
  - N Cover Letter for Submission of Original NDA Number 022368
  - O FDA Acknowledgment Letter for NDA Number 022368
  - P FDA Complete Response Letter for NDA Number 022368
  - Q Cover Letter for Complete Response Resubmission for NDA Number 022368
  - R FDA Filing Communication for NDA Number 022368
  - S Table of Correspondence History Between Applicant and the FDA

# Exhibit A

Your Ref: FBR 2173 P0010 US

Our Ref: 72184

26 August 1996

*VIA COURIER*

Dressler Goldsmith Milnamow & Katz Ltd  
Attn: Mr Allen J Hoover  
Two Prudential Plaza  
Suite 4700  
Chicago Illinois 60601  
UNITED STATES OF AMERICA

Dear Mr Hoover

Re: SANDRA DOREEN ANDERSON (ASSIGNEE CENTRAL SYDNEY AREA  
HEALTH SERVICE) - International Patent Application No PCT/AU95/00086)  
Entitled: "Method and device for the provocation of air passage narrowing and/or  
the induction of sputum"  
- and -  
National Phase in United States of America

---

We enclose the following documents duly executed for filing at the United States Patent  
Office:-

- Combined Declaration & Power of Attorney
- Assignment

Please acknowledge receipt of the documents by return mail.

Yours sincerely  
F.B. RICE & CO.

By: CHRIS O'SULLIVAN

COS/JAB/H26

72184

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: METHOD AND DEVICE FOR THE PROVOCATION OF AIR PASSAGE NARROWING AND OR THE INDUCTION OF SPUTUM

the specification of which (check only one item below):

- is attached hereto.
- was filed as United States application

Serial No. \_\_\_\_\_

on \_\_\_\_\_

and was amended

on \_\_\_\_\_ (if applicable).

- was filed as PCT international application

Number PCT/AU95/00086

on 23 February 1995 (23.02.95)

and was amended under PCT Article 19

on \_\_\_\_\_ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (If PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
Australia	PM4114	25 Feb. 1994 (25.02.94)	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §121, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS

STATUS (Check one)

U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATIONS DESIGNATING THE U.S.

PCT APPLICATION NO	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (if any)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (List name and registration number)

James E. Gauger, Jr., Reg. No. 38,154  
Stephen J. Goldmar, Reg. No. 846;  
Allen J. Hoover, Reg. No. 24,120;  
Martin L. Katz, Reg. No. 25,011;  
Annette M. McGarry, Reg. No. 34,671;  
John P. Milnamow, Reg. No. 20,635;

Lisa V. Mueller, Reg. No. 38,978;  
Thomas E. Northrup, Reg. No. 33,268;  
Paul M. Odell, Reg. No. 28,332;  
Jack Shoop, Reg. No. 17,551;  
Joel E. Siegel, Reg. No. 25,440;  
Paul M. Vargo, Reg. No. 29,116

Send Correspondence to:

Allen J. Hoover  
Dressler, Goldsmith, Milnamow & Katz, Ltd.  
Two Prudential Plaza, Suite 4700  
180 N. Stetson Ave., Chicago, IL 60601

Direct Telephone Calls to:  
(name and telephone number)

(312) 616-5400

201

202

203

FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	Anderson	Sandra	Doreen
RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	Birchgrove	Australia	Australia
POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
	31 Wharf Road	Birchgrove, N.S.W. 2041	Australia
FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201  
*X Helenz D. Anderson*

DATE  
*X 21st August 1996*

SIGNATURE OF INVENTOR 202

DATE

SIGNATURE OF INVENTOR 203

DATE

# Assignment

Serial No. \_\_\_\_\_

Filed: \_\_\_\_\_

**In Consideration** of One Dollar and other good and valuable considerations, the receipt of which is hereby acknowledged, the entire right, title and interest in the invention or improvements of the undersigned in METHOD AND DEVICE FOR THE PROVOCATION OF AIR PASSAGE NARROWING AND/OR THE INDUCTION OF SPUTUM, and in the application for Letters Patent of the United States therefor, executed by the undersigned concurrently herewith as the national phase of International Application No. PCT/AU95/00086, and in any reissue or extension of any Letters Patent that may be granted upon said application are hereby assigned by the undersigned to Central Sydney Area Health Service of Queen Elizabeth II Building, Level 1, Missenden Road, Camperdown, New South Wales 2050, Australia, and the successors, legal representatives and assigns of Central Sydney Area Health Service (hereinafter collectively called said Assignee), and the Commissioner of Patents and Trademarks is hereby authorized and requested by the undersigned to issue said Letters Patent to said Assignee.

**For said considerations** it is hereby agreed by the undersigned, upon the request of said Assignee, to execute any necessary and proper oaths or affidavits relating to said application or required for the filing or prosecution of any divisional or continuing application thereof or for the filing or prosecution of any application for the reissue or extension of any Letters Patent that may be granted on said invention or improvements that said Assignee may deem necessary or expedient, and for the said considerations it is further agreed by the undersigned, upon the request of said Assignee, in the event of said application or any division thereof, or Letters Patent issued thereon, or any reissue or application for the reissue thereof, becoming involved in Interference, to cooperate to the best of the ability of the undersigned with said Assignee in the matters of preparing and executing the preliminary statement and giving and producing evidence in support thereof, and further to perform, upon such request, any and all affirmative acts to obtain said Letters Patent and vest all rights therein hereby conveyed in the said Assignee as fully and entirely as the same would have been held and enjoyed by the undersigned if this assignment and sale had not been made. And for the said considerations the entire right, title and interest in said invention or improvements, including all priority rights, and the right to claim priority rights and the privileges and benefits thereof, including those under the International Convention, and all other Conventions, and the right to file applications for patent in said Assignee's own name for said invention or improvements in each and every country of the world are hereby assigned and granted by the undersigned to said Assignee. It is further agreed by the undersigned, upon the request of said Assignee, to execute any and all documents that shall be required of the undersigned to be executed in connection with any and all applications for foreign Letters Patent therefor, including the prosecution thereof, and to execute any and all documents necessary to invest title in said foreign applications and patents in said Assignee. The undersigned also further agrees, for the said considerations, upon the request of said Assignee, to promptly perform all lawful acts deemed by said Assignee to be necessary or advisable in connection with maintaining, enforcing, or transferring the resulting grants of said Letters Patent in the United States or foreign countries. It is agreed that such lawful acts include, but are not limited to, taking oaths, executing declarations, powers, taking oaths, executing assignments and other papers and giving testimony. The attorneys of record in such application for patent are hereby authorized and requested by the undersigned to insert in this Assignment the date and serial number thereof in the places provided therefor.

*x* Sandra Doreen Anderson (Seal)  
Sandra Doreen Anderson

Date: 21st August, 1996

# Exhibit B

PATENT LICENCE AGREEMENT made *10<sup>th</sup> October 2001*

BETWEEN

PRAXIS PHARMACEUTICALS AUSTRALIA PTY LTD (ACN 082 811 630) of 60  
Marcus Clarke Street, Canberra, ACT 2601 ('PRAXIS')

AND

CENTRAL SYDNEY AREA HEALTH SERVICE of QEII Building, RPAH Campus,  
Missenden Road, Camperdown NSW ('CSAHS')

RECITALS

- A. CSAHS has knowledge in respect of powder technologies for use in the management of respiratory disease. Aspects of this knowledge are protected by patents and patent applications in a number of countries.
- B. CSAHS proposes to provide the knowledge to PRAXIS and to enter into an exclusive licence with PRAXIS to allow PRAXIS to exploit the knowledge on the following terms and conditions.
- C. CSAHS also has an AusIndustry Start grant (GRA0078) related to the use of inhaled mannitol as a test for airway hyperresponsiveness. This grant is currently suspended.
- D. CSAHS proposes that PRAXIS enter into Start grant GRA0078 for the development of inhaled mannitol and assume the rights and obligations currently held by Rhone Poulenc Rorer, as part of this agreement.

AGREEMENT

Definitions

In this Agreement:

Redacted - confidential information

'CSAHS Intellectual Property' means the Patents, Additional Patents and Knowledge in respect of powder technologies.

Redacted - confidential information

Redacted - confidential information

'Patents' means patents and patent applications owned by CSAHS in the countries listed in Attachment 2 and such other patents applied for by CSAHS or Praxis which claims priority from any of those patents.

Redacted - confidential information

Redacted - confidential information

## Redacted - confidential information

### 4. Licences

- 4.1 CSAHS grants PRAXIS a worldwide exclusive sub-licensable licence to exploit the CSAHS Intellectual Property.

Redacted - confidential information

EXECUTED AS AN AGREEMENT

SIGNED for and on behalf of )  
PRAXIS PTY LIMITED by a duly )  
authorised director in the presence )  
of: )

*Aaron D. Robertson*

Signature of Authorised Person

*(Signature)*

LEWIS SCHULZ

Witness

*General Manager*

Title of Authorised Person

*A. D. ROBERTSON*

Name of Authorised Person

SIGNED for and on behalf of )  
CENTRAL SYDNEY AREA )  
CSAHS by its Chief Executive )  
Officer Dr Diana G )  
Horvath in the presence of: )

*Diana Horvath*

Witness

*M. Wallace*

Michael Wallace  
CEO CSAHS

Attachment 1: Knowledge in respect of powder technologies  
Attachment 2: Patents

**ATTACHMENT 1  
EXISTING KNOWLEDGE**  
**for mannitol as a Diagnostic Test for bronchial hyperresponsiveness and  
for the therapeutic use of mannitol to increase mucociliary clearance**

**Redacted - confidential information**

**Redacted - confidential information**

Redacted - confidential information

**Redacted - confidential information**

**Attachment 2**

<b>Country</b>	<b>Official Number (Patent or Application)</b>
Australia	682756
Canada	2183471
Europe (EPO)	95910331.8
Japan	7-522021
Malaysia	PI9603590
New Zealand	281522
Peoples Republic Of China	95191808.7
Republic Of Korea	96-704666
Singapore	34525
The Philippines	I-54034
United States Of America	5817028
Viet Nam	SC0131/96
<b>TOTAL</b>	

Redacted - confidential information

# Exhibit C

**ASIC**Australian Securities & Investments  
Commission**National Names  
Index**Index of corporate and  
business names

SEARCH TIPS

Extracted from ASIC's database at AEST 10:48:30 on 07/05/2010

**Name** PHARMAXIS LTD**ACN** 082 811 630**ABN** 75 082 811 630**Type** Australian Public Company, Limited By Shares**Registration Date** 29/05/1998**Next Review Date** 29/05/2010**Status** Registered**Locality of Registered Office** Frenchs Forest NSW 2086**Jurisdiction** Australian Securities & Investments Commission**Former Name(s)** PHARMAXIS PTY LTD

PRAXIS PHARMACEUTICALS AUSTRALIA PTY LIMITED

These are the documents that ASIC has most recently received from or in relation to this organisation. Page numbers are shown if processing is complete and the document is available for purchase.

**Date Number Pages Description**

30/04/2010	5E2356930	10	7053A Disclosure Notice - Ex Australian Stock Exchange 06013 ASX - Appendix 3b
27/04/2010	5E2352019	2	7053A Disclosure Notice - Ex Australian Stock Exchange 11002 ASX Progress Report - Other 12008 ASX Company Administration - Other
23/04/2010	5E2351772	10	7053A Disclosure Notice - Ex Australian Stock Exchange 06013 ASX - Appendix 3b

 Complete Document Listing Document Listing Between DatesExclude form 7053A (Disclosure notice for disclosing entity) Start Date  May  End Date  May  Biller Code: 17301  
Ref: 2290828116306Billpay Code: 8929  
Ref: 2290 8281 1630 625  
 by phone 13 18 16  
 pay by Mastercard or VISAinternet [postbillpay.com.au](http://postbillpay.com.au)



pay by Mastercard or VISA

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To give us your comments send feedback to [research@asic.gov.au](mailto:research@asic.gov.au).

# Exhibit D

## Orders



New South Wales

# Health Services (Amalgamation of Area Health Services) Order 2004

under the

Health Services Act 1997

MARIE BASHIR, Governor

I, Professor Marie Bashir AC, Governor of the State of New South Wales, with the advice of the Executive Council, and in pursuance of section 20 (1) of the *Health Services Act 1997*, make the following Order.

Dated, this 20th day of October 2004.

By Her Excellency's Command,

MORRIS IEMMA, M.P.,  
Minister for Health

### Explanatory note

The object of this Order is to amalgamate the area health services listed in Schedule 1 to the *Health Services Act 1997*. The area health services listed in Column 2 are amalgamated into the area health services listed in Column 1.

<b>Column 1</b>	<b>Column 2</b>
<b>Amalgamated area health service</b>	<b>Old area health services</b>
Greater Southern Area Health Service	Greater Murray Area Health Service Southern Area Health Service
Greater Western Area Health Service	Far West Area Health Service Macquarie Area Health Service Mid Western Area Health Service
Hunter and New England Area Health Service	Hunter Area Health Service New England Area Health Service

Health Services (Amalgamation of Area Health Services) Order 2004

Explanatory note

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<b>Column 1</b>	<b>Column 2</b>
<b>Amalgamated area health service</b>	<b>Old area health services</b>
North Coast Area Health Service	Mid North Coast Area Health Service Northern Rivers Area Health Service
Northern Sydney and Central Coast Area Health Service	Central Coast Area Health Service Northern Sydney Area Health Service
South Eastern Sydney and Illawarra Area Health Service	Illawarra Area Health Service South Eastern Sydney Area Health Service
Sydney South West Area Health Service	Central Sydney Area Health Service South Western Sydney Area Health Service
Sydney West Area Health Service	Wentworth Area Health Service Western Sydney Area Health Service

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This Order is made under section 20 (1) of the *Health Services Act 1997*.

Health Services (Amalgamation of Area Health Services) Order 2004

Clause 1

**Health Services (Amalgamation of Area Health Services)  
Order 2004**

under the

Health Services Act 1997

**1 Name of Order**

This Order is the *Health Services (Amalgamation of Area Health Services) Order 2004*.

**2 Commencement**

This Order commences on 1 January 2005.

**3 Amalgamation of area health services**

The area health services listed below in Column 2 are amalgamated to form the area health services listed opposite in Column 1:

<b>Column 1</b>	<b>Column 2</b>
<b>Amalgamated area health service</b>	<b>Old area health services</b>
Greater Southern Area Health Service	Greater Murray Area Health Service Southern Area Health Service
Greater Western Area Health Service	Far West Area Health Service Macquarie Area Health Service Mid Western Area Health Service
Hunter and New England Area Health Service	Hunter Area Health Service New England Area Health Service
North Coast Area Health Service	Mid North Coast Area Health Service Northern Rivers Area Health Service
Northern Sydney and Central Coast Area Health Service	Central Coast Area Health Service Northern Sydney Area Health Service
South Eastern Sydney and Illawarra Area Health Service	Illawarra Area Health Service South Eastern Sydney Area Health Service

Clause 4      Health Services (Amalgamation of Area Health Services) Order 2004

Column 1	Column 2
<b>Amalgamated area health service</b>	<b>Old area health services</b>
Sydney South West Area Health Service	Central Sydney Area Health Service South Western Sydney Area Health Service
Sydney West Area Health Service	Wentworth Area Health Service Western Sydney Area Health Service

#### 4 Amendment of Health Services Act 1997

The *Health Services Act 1997* is amended as set out in Schedule 1.

## Health Services (Amalgamation of Area Health Services) Order 2004

Amendment

Schedule 1

**Schedule 1      Amendment**

(Clause 4)

**Schedule 1 Names and areas of area health services**

Omit Columns 1, 2 and 3. Insert instead:

<b>Column 1</b>	<b>Column 2</b>	<b>Column 3</b>
<b>Name of service</b>	<b>Description of local government area or city</b>	<b>Description of area other than local government area</b>
Greater Southern Area Health Service	Albury Bega Valley Berrigan Bland Bombala Boorowa Carrathool Conargo Coolamon Cooma-Monaro Cootamundra Corowa Deniliquin Eastern Capital City Regional Eurobodalla Greater Argyle Greater Hume Greater Queanbeyan Griffith Gundagai Harden Hay Jerilderie Junee Lecton Lockhart	

## Health Services (Amalgamation of Area Health Services) Order 2004

## Schedule 1      Amendment

Column 1 <b>Name of service</b>	Column 2 <b>Description of local government area or city</b>	Column 3 <b>Description of area other than local government area</b>
	Murray	
	Murrumbidgee	
	Narrandera	
	Snowy River	
	Temora	
	Tumbarumba	
	Tumut	
	Upper Lachlan	
	Urana	
	Wagga Wagga	
	Wakool	
	Yass Valley	
	Young	
Greater Western Area Health Service	Balranald	Unincorporated area
	Bathurst Regional	
	Blayney	
	Bogan	
	Bourke	
	Brewarrina	
	Broken Hill	
	Cabonne	
	Central Darling	
	Cobar	
	Coolah	
	Coonabarabran	
	Coonamble	
	Cowra	
	Dubbo	
	Forbes	
	Gulgandra	
	Lachlan	
	Mid-Western Regional	
	Narramine	
	Oberon	

## Health Services (Amalgamation of Area Health Services) Order 2004

Amendment

Schedule 1

Column 1 <b>Name of service</b>	Column 2 <b>Description of local government area or city</b>	Column 3 <b>Description of area other than local government area</b>
	Orange	
	Parkes	
	Walgett	
	Warren	
	Weddin	
	Wellington	
	Wentworth	
Hunter and New England Area Health Service	Armidale Dumaresq Cessnock Dungog Glen Innes Severn Gloucester Great Lakes Greater Taree Gunnedah Guyra Gwydir Inverell Lake Macquarie Liverpool Plains Maitland Moree Plains Muswellbrook Narrabri Newcastle Port Stephens Singleton Tamworth Regional Tenterfield Upper Hunter Uralla Walcha	

## Health Services (Amalgamation of Area Health Services) Order 2004

## Schedule 1      Amendment

<b>Column 1</b>	<b>Column 2</b>	<b>Column 3</b>
<b>Name of service</b>	<b>Description of local government area or city</b>	<b>Description of area other than local government area</b>
North Coast Area Health Service	Ballina Bellinger Byron Clarence Valley Coffs Harbour Hastings Kempsey Kyogle Lismore Nambucca Richmond Valley Tweed	
Northern Sydney and Central Coast Area Health Service	Gosford Hornsby Hunters Hill Ku-ring-gai Lane Cove Manly Mosman North Sydney Pittwater Ryde Warringah Willoughby Wyong	
South Eastern Sydney and Illawarra Area Health Service	Botany Bay Hurstville Kiama Kogarah Randwick Rockdale Shellharbour Shoalhaven Sutherland	Lord Howe Island

## Health Services (Amalgamation of Area Health Services) Order 2004

Amendment

Schedule 1

Column 1	Column 2	Column 3
Name of service	Description of local government area or city	Description of area other than local government area
Sydney South West Area Health Service	Sydney (part) Waverley Woolrahra Wollongong  Ashfield Bankstown Burwood Camden Campbelltown Canada Bay Canterbury Fairfield Leichhardt Liverpool Marrickville Strathfield Sydney (part) Wingecarribee Wollondilly	
Sydney West Area Health service	Auburn Baulkham Hills Blacktown Blue Mountains Hawkesbury Holroyd Lithgow Parramatta Penrith	

# Exhibit E



# New South Wales Consolidated Acts

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## HEALTH SERVICES ACT 1997 - SCHEDULE 4

### SCHEDULE 4 – Transfers, dissolutions, amalgamations and changes of name or nature of governance

(Sections 21, 44, 64 and 132)

#### Part 1 - General

##### Division 1 - Interpretation

###### 1 Definitions

In this Schedule:

"instrument" means an instrument (other than this Act) that creates, modifies or extinguishes rights or liabilities (or would do so if lodged, filed or registered in accordance with any law), and includes any judgment, order or process of a court.

"transferee" means the person or body to which any staff, assets, rights or liabilities are transferred.

"transferor" means the person or body from which any staff, assets, rights or liabilities are transferred.

"transferred public health organisation" means a public health organisation that is transferred to another public health organisation.

###### 2 Orders to which this Schedule applies

This Schedule applies to the following orders:

- (a) an order under section 20 (Dissolution, amalgamation or change of name of area health services),
- (b) an order under section 43 (Dissolution, transfer, amalgamation, or change of name or nature of governance of statutory health corporations),
- (c) an order under section 64 (Transfer of recognised establishments and recognised services of affiliated health organisations),
- (d) an order under section 131 (Transfer of hospitals, health institutions, services and property between area health services and statutory health corporations).

##### Division 2 - Consequences of orders to which this Schedule applies

###### 3 Orders relating to area health services

- (1) Dissolution orders On and from the date specified in an order under section 20 (1)
  - (a) for the dissolution of an area health service:

- (a) the area health service is dissolved, and

(c) the assets, rights and liabilities of the area health service are transferred to the Minister (or any other person or body specified in the order), and

(d) Part 2 applies to that transfer.

(2) Amalgamation orders On and from the date specified in an order under section 20  
(1) (b) for the amalgamation of 2 or more area health services:

(a) each area health service amalgamated by the order is dissolved, and

(c) the assets, rights and liabilities of each amalgamating service are transferred to the amalgamated area health service, and

(d) Part 2 applies to that transfer.

(3) Name change orders On and from the date specified in an order made under section 20 (1) (c) changing the name of an area health service, Part 3 applies to that change of name.

(4) Effect on compensation rights Nothing in this Schedule affects any compensation rights to which the chief executive of a dissolved or amalgamating area health service may be entitled under Part 3 of Chapter 9 as a consequence of ceasing to hold office.

#### **4 Orders relating to statutory health corporations**

(1) Dissolution orders On and from the date specified in an order made under section 43  
(1) (a) dissolving a statutory health corporation:

(a) the statutory health corporation is dissolved, and

(b) in the case of a board governed health corporation, the members of the board cease to hold office, but are not entitled to be paid any compensation by reason of ceasing to hold office, and

(c) the assets, rights and liabilities of the statutory health corporation are transferred to the Minister (or any other person or body specified in the order), and

(d) Part 2 applies to that transfer.

(2) Transfer orders On and from the date specified in an order made under section 43 (1)  
(b) transferring a statutory health corporation to an area health service:

(a) the statutory health corporation is dissolved, and

(b) in the case of a board governed health corporation, the members of the board cease to hold office, but are not entitled to be paid any compensation by reason of ceasing to hold office, and

(c) the assets, rights and liabilities of the statutory health corporation are transferred to the area health service, and

(d) Part 2 applies to that transfer.

(3) Amalgamation orders On and from the date specified in an order made under section 43 (1) (c) for the amalgamation of 2 or more statutory health corporations:

(a) each statutory health corporation amalgamated by the order is dissolved, and

(b) the members of any board governed health corporation involved in the amalgamation cease to hold office, and:

(i) if the amalgamated corporation is a board governed health corporation, are eligible (if otherwise qualified) to be appointed as members of the board of the amalgamated corporation, and

(ii) are not entitled to be paid any compensation by reason of ceasing to hold office, and

(c) the assets, rights and liabilities of each amalgamating service are transferred to the amalgamated statutory health corporation, and

(d) Part 2 applies to that transfer.

(4) Name change orders On and from the date specified in an order made under section 43 (1) (d) changing the name of a statutory health corporation, Part 3 applies to that change of name.

(4A) Change of governance orders On and from the date specified in an order made under section 43 (1) (d) changing the nature of governance of a statutory health corporation from board governance to chief executive governance, the members of the board for the corporation cease to hold office, but are not entitled to be paid any compensation by reason of ceasing to hold office.

(5) Effect on compensation rights Nothing in this section affects any compensation rights to which the chief executive of a dissolved or amalgamating statutory health corporation may be entitled under Part 3 of Chapter 9 of this Act or Part 3.1 of the Public Sector Employment and Management Act 2002 as a consequence of ceasing to hold office as such.

## **5 Orders relating to affiliated health organisations**

(1) Transfer of hospitals and health institutions On and from the date specified in an order under section 64 (1) (a) transferring any public hospital or health institution of an affiliated health organisation that is a recognised establishment of the organisation to an area health service or statutory health corporation, Part 2 has effect to the extent of that transfer.

(2) Transfer of health services and health support services On and from the date specified in an order under section 64 (1) (b) transferring any health service or health support service of an affiliated health organisation that is a recognised service of the organisation to an area health service or statutory health corporation, Part 2 has effect to the extent of that transfer.

(3) Transfer of assets, rights or liabilities On and from the date specified in an order under section 64 (1) (c) transferring any assets, rights or liabilities of an affiliated health organisation relating to a recognised establishment or recognised service of the

organisation to an area health service or statutory health corporation, Part 2 has effect to the extent of that transfer.

(4) **Consents to transfers of property** An order under section 64 (1) that purports to transfer any property of an affiliated health organisation operates to transfer only such property in respect of the transfer of which the organisation has consented.

(5) **Effect on trustees of transfer order** If any such order operates to transfer all of the property of an affiliated health organisation that is held in trust for it by trustees, the trustees cease to hold office as trustees in respect of that property on and from the transfer date specified in the order.

## **6 Orders transferring hospitals, health institutions, services or property between area health organisations and statutory health corporations**

(1) **Transfer of public hospitals and health institutions** On and from the date specified in an order under section 131 (1) (a) transferring any public hospital or health institution under the control of a statutory health organisation to another statutory health organisation, Part 2 has effect to the extent of that transfer.

(2) **Transfer of health services and health support services** On and from the date specified in an order under section 131 (1) (b) transferring any health service or health support service under the control of a statutory health organisation to another statutory health organisation, Part 2 has effect to the extent of that transfer.

(3) **Transfer of services provided by Crown** On and from the date specified in an order under section 131 (1) (c) transferring any hospital or health service controlled by the Crown, Part 2 has effect to the extent of that transfer.

(4) **Transfer of assets, rights or liabilities** On and from the date specified in an order under section 131 (1) (d) transferring any assets, rights or liabilities of a statutory health organisation to another statutory health organisation, Part 2 has effect to the extent of that transfer.

## **Part 2 - Transfers**

### **Division 1 - Staff**

#### **7 Transfer of staff**

A member of staff who is transferred by a transfer to which this Part applies is (until other provision is duly made under any Act or law) to be employed in accordance with any relevant statutory provisions, awards, agreements and determinations that would have applied to the person had the person not been transferred but remained a member of staff of the transferor.

### **Division 2 - Transfer of hospitals, health institutions, health services and health support services**

#### **8 Transfer of hospitals and health institutions**

(1) An order that transfers a hospital or health institution from any public health organisation to another public health organisation is taken to transfer (unless the order provides otherwise):

- (a) the staff employed in or in connection with the hospital or institution, and
  - (b) the assets, rights and liabilities used principally for the conduct of the hospital or institution.
- (2) An order that transfers a hospital or health institution controlled by the Crown to a public health organisation is taken (unless the order provides otherwise) to transfer the personal property of the Crown used principally for the conduct of the hospital or institution.

## **9 Transfer of health services and health support services**

An order that transfers a health service or health support service from any public health organisation to another public health organisation may specify the staff, assets, rights or liabilities of that health service or health support service that are to be transferred from the other public health organisation along with the health service or health support service.

## **Division 3 - Assets, rights or liabilities**

### **10 Vesting of undertaking in transferee**

- (1) When any assets, rights or liabilities are transferred by a transfer to which this Part applies, the following provisions have effect:
- (a) the assets of the transferor vest in the transferee by virtue of this clause and without the need for any further conveyance, transfer, assignment or assurance,
  - (b) the rights or liabilities of the transferor become by virtue of this clause the rights or liabilities of the transferee,
  - (c) all proceedings relating to the assets, rights or liabilities commenced before the transfer by or against the transferor or a predecessor of the transferor and pending immediately before the transfer are taken to be proceedings pending by or against the transferee,
  - (d) any act, matter or thing done or omitted to be done in relation to the assets, rights or liabilities before the transfer by, to or in respect of the transferor is (to the extent to which that act, matter or thing has any force or effect) taken to have been done or omitted by, to or in respect of the transferee,
  - (d1) the transferee has all the entitlements and obligations of the transferor in relation to those assets, rights and liabilities that the transferor would have had but for the order, whether or not those entitlements and obligations were actual or potential at the time the transfer took effect,
  - (e) a reference in any Act, in any instrument made under any Act or in any document of any kind to the transferor or a predecessor of the transferor is (to the extent to which it relates to those assets, rights or liabilities) taken to include a reference to the transferee.
- (2) The operation of this clause is not to be regarded:

- (a) as a breach of contract or confidence or otherwise as a civil wrong, or
  - (b) as a breach of any contractual provision prohibiting, restricting or regulating the assignment or transfer of assets, rights or liabilities, or
  - (c) as giving rise to any remedy by a party to an instrument, or as causing or permitting the termination of any instrument, because of a change in the beneficial or legal ownership of any asset, right or liability, or
  - (d) as an event of default under any contract or other instrument.
- (3) No attornment to the transferee by a lessee from the transferor is required.
- (4) A transfer is subject to the terms and conditions of the order by which it is effected.
- (5) No compensation is payable to any person or body in connection with a transfer to which this Part applies except to the extent (if any) to which the order giving rise to the transfer so provides.
- (6) Subclause (5) does not affect the rights of any member of staff who is the subject of a transfer to which this Part applies.

#### **Division 4 - Other general provisions concerning transfers**

##### **11 Date of vesting**

A transfer to which this Part applies takes effect on the date specified in the order by which it is effected.

##### **12 Consideration for vesting**

The Minister may, by order in writing, specify the consideration on which a transfer to which this Part applies is made and the value or values at which the assets, rights or liabilities are transferred.

##### **13 Stamp duty**

Stamp duty is not chargeable for or in respect of:

- (a) a transfer to which this Part applies, or
- (b) anything certified by the Minister as having been done in consequence of such a transfer (for example, the transfer or conveyance of an interest in land).

##### **14 Confirmation of vesting**

- (1) The Minister may, by notice in writing, confirm a transfer of particular assets, rights or liabilities by operation of this Part.
- (2) Such a notice is conclusive evidence of that transfer.

##### **15 By-laws of public health organisation**

The by-laws of a transferred public health organisation in force at the transfer date continue to apply to and in respect of any hospital, health institution, health service or health support service it

conducts or provides until by-laws are made under this Act by the transferee in relation to that hospital, institution or service.

## **16 Functions of transferred public health organisation**

(1) Any function conferred or imposed immediately before the transfer date on a transferred public health organisation, or on the board (or managing body) of a public health organisation, in relation to the administration and operation of any of the hospitals, health institutions, health services or health support services it conducts or provides may continue to be exercised on and from the transfer date by the transferee.

(2) Subclause (1) has effect despite any other provision of this Act.

(3) Without limiting subclause (1), a reference in that subclause to a function includes a reference to a power of investment.

## **Part 3 - Changes of name**

### **17 Name changes do not affect status of service**

A change of name of an area health service or a statutory health corporation by an order does not operate:

(a) to create a new legal entity, or

(b) to prejudice or affect the identity of the body corporate constituted as an area health service or statutory health corporation or its continuity as a body corporate, or

(c) to affect the property, or the rights or obligations, of the area health service or statutory health corporation, or

(d) to render defective any legal proceedings by or against the area health service or statutory health corporation,

and any legal proceedings that could have been continued or commenced by or against the area health service or statutory health corporation by its former name may be continued or commenced by or against it by its new name.

## **Part 4 - Savings and transitional regulations**

### **18 Regulations**

(1) The regulations may contain other provisions of a savings or transitional nature consequent on the making of an order to which this Schedule applies.

(1A) Without limiting subclause (1), a provision referred to in that subclause may make provision for or with respect to the legal consequences of the differential transfer of rights, obligations or other liabilities under the same contract or other agreement to more than one transferee.

(2) A provision referred to in subclause (1) which relates to a particular order may, if the regulations so provide, take effect as from the date of the order or a later day.

(3) To the extent to which a provision referred to in subclause (1) takes effect from a date that is earlier than the date of its publication in the Gazette, the provision does not operate so as:

- (a) to affect, in a manner prejudicial to any person (other than the State, an authority of the State, an area health service or a statutory health corporation), the rights of that person existing before the date of its publication in the Gazette, or
- (b) to impose liabilities on any person (other than the State, an authority of the State, an area health service or a statutory health corporation) in respect of anything done or omitted to be done before the date of its publication in the Gazette.

(4) A provision referred to in subclause (1) has, if the regulations so provide, effect despite any other clause of this Schedule.

# Exhibit F



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 22368

**NDA APPROVAL**

Pharmaxis, Inc.  
One East Uwchlan Avenue  
Suite 405  
Exton, PA 19341

Attention: Valerie Waltman, MS  
Senior Manager, Regulatory Affairs

Dear Ms. Waltman:

Please refer to your New Drug Application (NDA) dated April 7, 2010, received April 7, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aridol (mannitol inhalation powder).

We acknowledge receipt of your amendments dated August 6, 26, and 27, and September 24, 2010.

The April 7, 2010, submission constituted a complete response to our December 23, 2009, action letter.

This new drug application provides for the use of Aridol (mannitol inhalation powder) for the assessment of bronchial hyperresponsiveness in patients > 6 years of age who do not have clinically apparent asthma.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text with the minor editorial revisions listed below:

1. Remove the Drug Interactions Section from the HIGHLIGHTS OF PRESCRIBING INFORMATION
2. Replace "Adolescent" with "Adolescents" in Section 6.1, ADVERSE REACTIONS, Clinical Trials Experience, Children and Adolescents Aged 6-17 Years

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is

identical, except with the revisions listed, to the enclosed labeling text for the package insert and clinician instructions. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

#### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted September 23, 2010, received September 24, 2010, and blister pack submitted August 25, 2010, received on August 26, 2010, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 22368**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

#### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to less than six years of age because necessary studies are impossible or highly impracticable. This is because of the inability of children in this age range to adequately perform the required test.

We note that you have fulfilled the pediatric study requirement for ages six to 17 years for this application.

#### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify any unexpected serious risks in patients > 50 years of age with co-morbid conditions common in older populations.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify any unexpected serious risks in patients > 50 years of age with co-morbid conditions common in older populations.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 1667-1 A clinical trial with Aridol (mannitol inhalation powder) in subjects/patients older than 50 years of age who have significant co-morbidities common in an elderly population (e.g., COPD, obesity, cardiac risk factors, etc.) or reanalyze the data from completed clinical trials in which Aridol (mannitol inhalation powder) was administered to an elderly population with co-morbidities. A substantial number of the total population should be 65 years of age or greater. The trial should include the following objectives: 1) evaluate the degree of bronchoconstriction defined as a fall in FEV1 in the older subject/patient population and 2) evaluate the overall adverse event profile in subjects over 50 years of age.

The timetable you submitted on August 26, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	March 31, 2012
Trial Completion Date:	September 30, 2013
Final Report Submission:	February 28, 2014

Submit the protocol to your IND 70277, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments in your submission dated August 27, 2010. These commitments are listed below.

- 1667-2 The proposed specifications for foreign particulate matter are interim specifications. Test for foreign particulate matter in the first six U.S. commercial batches of Aridol (mannitol inhalation powder) and evaluate the results from this testing to either remove or finalize the foreign particulate drug product specifications. Submit this data to the Agency as a changes-being-effected supplement.

Final Report Submission: July 2012

- 1667-3 The proposed specifications for the Aerodynamic Particle Size Distribution (APSD) are interim specifications. Revise the APSD specifications based on the first ten U.S. commercial batches of ARIDOL Aridol (mannitol inhalation powder) and submit the revised specifications to the Agency as a prior-approval supplement.

Final Report Submission: July 2013

Submit clinical protocols to your IND 70277 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,” or “Postmarketing Commitment Correspondence.”

**PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

#### **LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program  
Office of Special Health Issues  
Food and Drug Administration  
10903 New Hampshire Ave  
Building 32, Mail Stop 5353  
Silver Spring, MD 20993

#### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Miranda Raggio, Senior Regulatory Project Manager, at (301) 796-2109.

Sincerely,

*(See appended electronic signature page)*

Badrul A. Chowdhury, M.D., Ph.D.  
Division Director

Division of Pulmonary, Allergy, and  
Rheumatology Products  
Office of Drug Evaluation II  
Office of New Drugs  
Center for Drug Evaluation and Research

**ENCLOSURE(S):**

**Content of Labeling**

Carton and Container, 9-24-10 version

Blister Pack, 8-26-10 version

Package Insert, 9-24-10 version

Clinician Instructions for use, 9-24-10 version

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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BADRUL A CHOWDHURY

10/05/2010

# Exhibit G



US005817028A

**United States Patent** [19]**Anderson**

**Patent Number:** **5,817,028**  
**Date of Patent:** **Oct. 6, 1998**

- [54] **METHOD AND DEVICE FOR THE PROVOCATION OF AIR PASSAGE NARROWING AND/OR THE INDUCTION OF SPUTUM**

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5,642,728	7/1997	Andersson et al.	.....	128/203.15
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- [75] Inventor: **Sandra Doreen Anderson**, Birchgrove, Australia

**FOREIGN PATENT DOCUMENTS**

- [73] Assignee: **Central Sydney Area Health Service, Camperdown, Australia**

1297012	12/1991	Canada .
177783	4/1992	European Pat. Off. .
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WO87/05213	3/1983	WIPO .
WO91/11179	2/1987	WIPO .
WO94/17822	2/1994	WIPO .

- [21] Appl. No.: **696,987**

**OTHER PUBLICATIONS**

- [22] PCT Filed: **Feb. 23, 1995**

European Journal of Respiratory Diseases, vol. 66(2), 1985, B.G. Simonsson et al., Acute and long-term airway hyperactivity in aluminum-salt exposed workers with nocturnal asthma.

- [86] PCT No.: **PCT/AU95/00086**

§ 371 Date: **Nov. 4, 1996**

§ 102(e) Date: **Nov. 4, 1996**

- [87] PCT Pub. No.: **WO95/22993**

PCT Pub. Date: **Aug. 31, 1995**

**[30] Foreign Application Priority Data**

Feb. 25, 1994 [AU] Australia ..... PM4114

- [51] Int. Cl.<sup>6</sup> ..... **A61M 11/00**

- [52] U.S. Cl. ..... **600/529, 128/200.14; 128/200.23**

- [58] Field of Search ..... **128/716, 725, 128/724, 720, 200.14, 200.23, 200.24, 200.25; 600/3, 529, 533, 537, 535**

Primary Examiner—Max Hindenburg

Assistant Examiner—Stephen Huane

Attorney, Agent, or Firm—Rockey, Milnamow & Katz, Ltd.

[57]

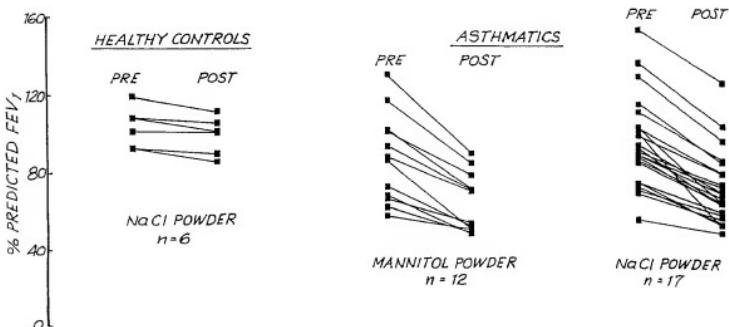
**ABSTRACT**

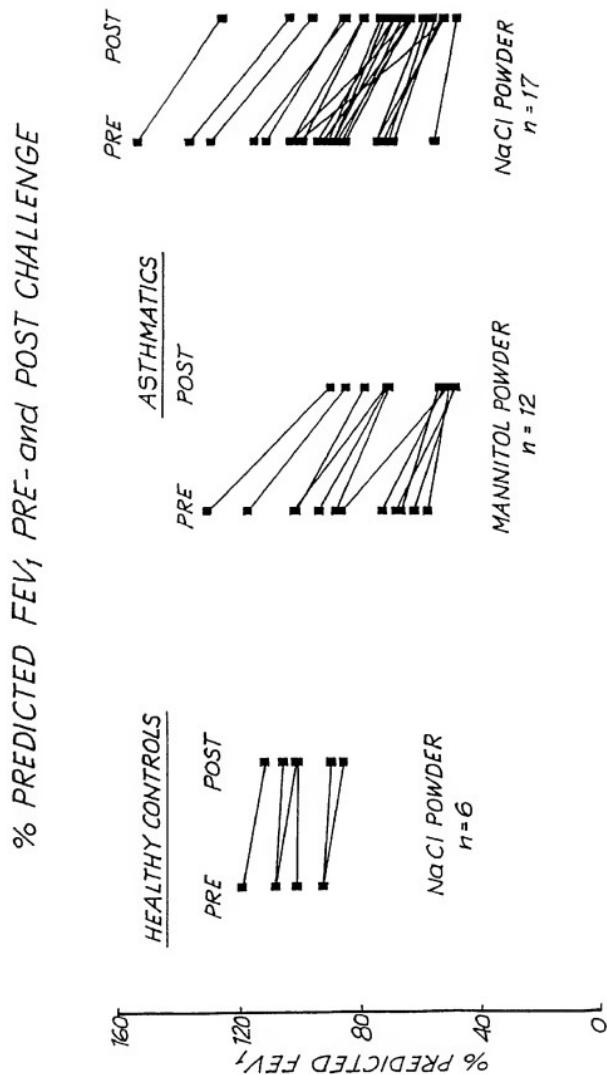
A method as described for testing the susceptibility of a person to asthma. The person inhales an effective amount of sodium chloride, mannitol or another substance capable of altering the osmolarity of airway surface liquid in the subject. The substance is in the form of a dispersible dry powder containing an effective proportion of particles of a respirable size. The subject is then measured to detect airway narrowing which is indicative of a propensity for asthma. The same technique of dry powder inhalation can be used to test for the susceptibility of a person to rhinitis, to induce sputum and promote mucociliary clearance.

**21 Claims, 4 Drawing Sheets**

**[56] References Cited****U.S. PATENT DOCUMENTS**

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**% PREDICTED FEV<sub>1</sub> PRE- and POST CHALLENGE**



DOSE OF DRY POWDER IN RELATION TO THE DOSE  
OF WET AEROSOL REQUIRED TO CAUSE AN ASTHMATIC RESPONSE

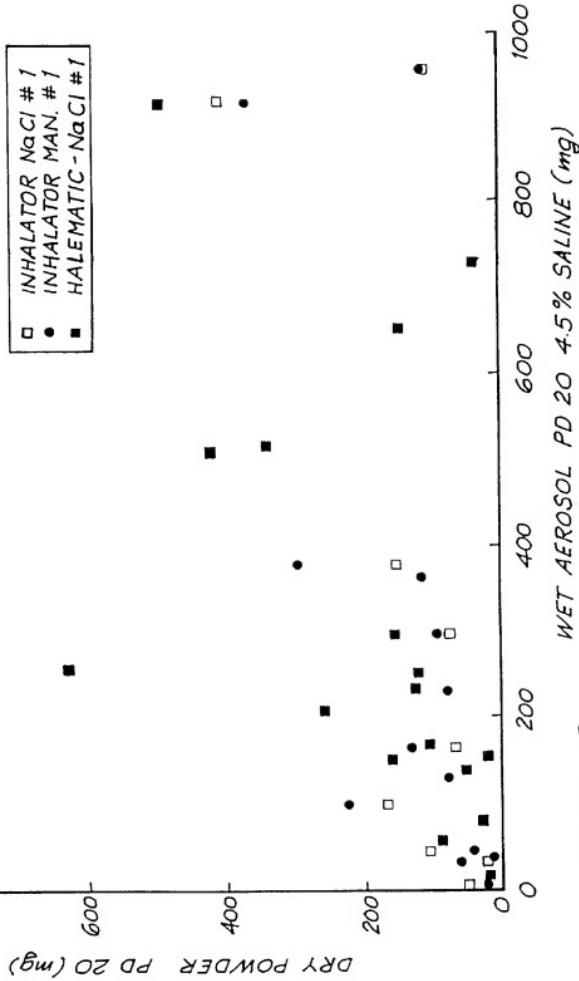
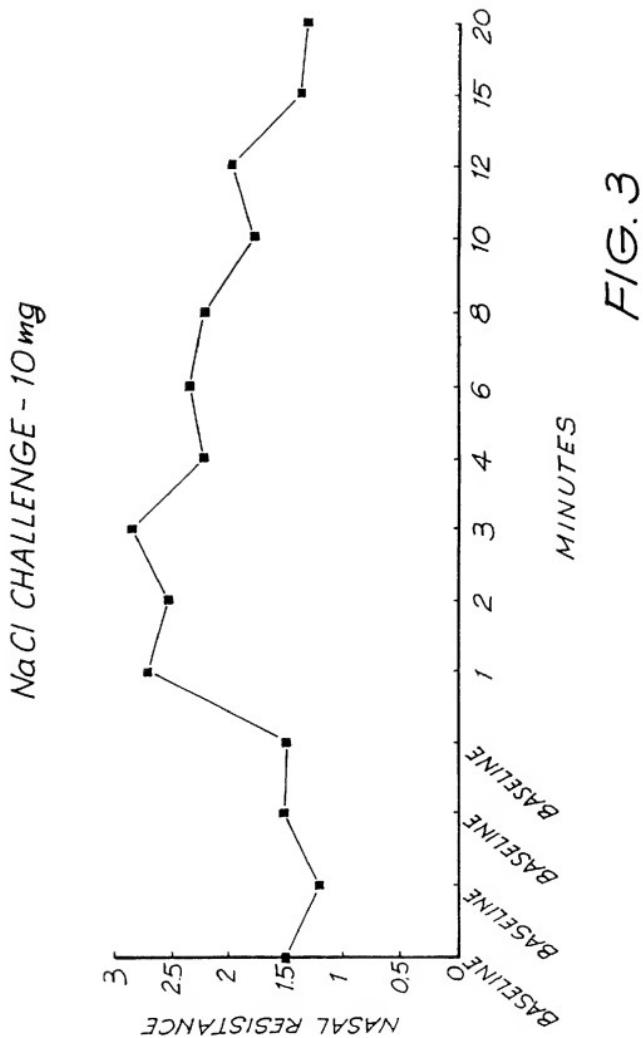


FIG. 2



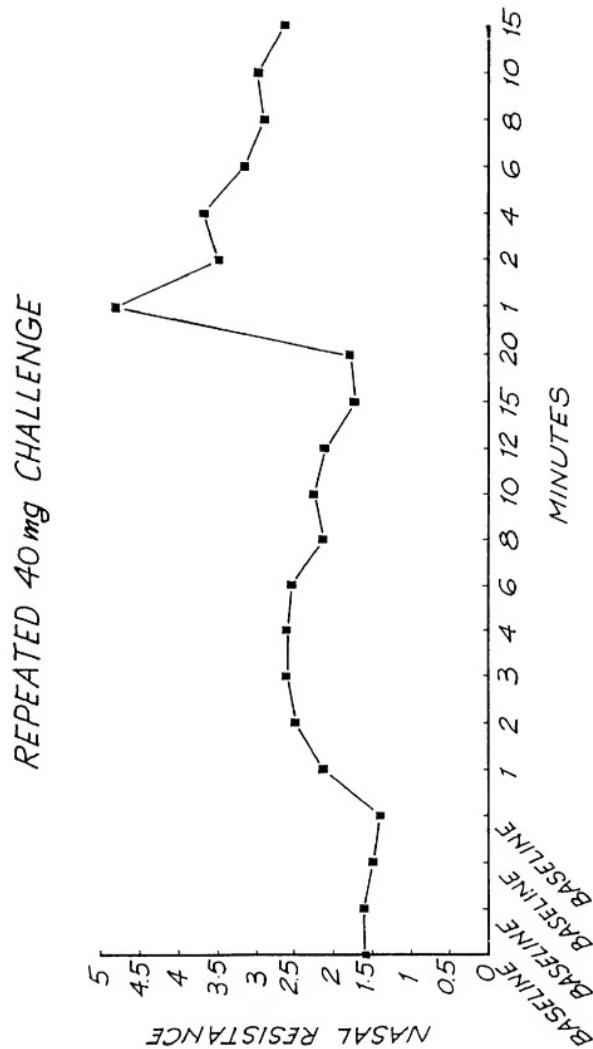


FIG. 4

**METHOD AND DEVICE FOR THE PROVOCATION OF AIR PASSAGE NARROWING AND/OR THE INDUCTION OF SPUTUM**

**FIELD OF THE INVENTION**

The present invention relates to a method and device useful to provoke airway narrowing and/or the induction of sputum. More particularly the invention relates to the use of dry powdered substances to induce a change in the osmolarity of the airways to induce narrowing and/or the induction of sputum.

**BACKGROUND ART**

Asthma is a chronic inflammatory disease of the airways resulting in bronchial hyperresponsiveness to a wide variety of chemical, physical, and allergenic stimuli. This sensitivity is manifested by narrowing of the airways and a reduction in the forced expiratory volume in one second (FEV<sub>1</sub>). Bronchial provocation testing, measuring changes in FEV<sub>1</sub> in response to inhaled stimuli, is well established as a technique for identifying and assessing the severity of airway hyperresponsiveness in persons suspected of having asthma (J Allergy Clin Immunol 1979; 64:1-250, Sterk et al Eur Respir J 1993,6(Supp 16):53-83). The most commonly used provocative agents are histamine and methacholine that act directly on specific receptors in the airways causing bronchial smooth muscle contraction. Challenges with these agents have a high negative predictive value but a low specificity for asthma when performed in a random population. Recently there have been problems with availability of these agents and accreditation for their use in humans. Currently the only product approved for human use by the Federal Drug Administration in the USA is Provoline (Hoffman La Roche) which is methacholine chloride.

Bronchial provocation testing with dry powders containing respirable particles of allergens (e.g. flour, red cedar wood dust, resins, gums) has also been used to identify specific allergens in order to establish a relationship between exposure to the suspected agent and the onset of asthma. These are most commonly used to investigate occupational asthma.

In the last 10 years the inventor's laboratory has developed and standardised a bronchial provocation test using wet aerosols of hyperosmolar saline generated by an ultrasonic nebuliser (Anderson et al., in, Provocation Testing in Clinical Practice, pp 249-278, Marcel Dekker Inc. 1994). This test is now well established in Laboratories throughout Australia and is listed in the Medical Benefits Schedule Book. This challenge test is also included in the report of the working party of the European Community for Steel and Coal (Sterk et al., Eur Respir J, 1993,6(Supp 16):53-83). It has recently been recommended by the Bronchial Provocation Committee of the International Study of Asthma and Allergy in Children.

Hyperosmolar saline challenge appears to be a very useful technique to identify persons with current asthma and those who suffer exercise-induced asthma. It is also very useful to evaluate the drugs used in the treatment of asthma.

The major disadvantage of using wet aerosols of hyperosmolar saline is that an ultrasonic nebuliser is required and this is expensive. Another disadvantage is that ultrasonic nebulisers require maintenance for cleaning and sterilisation. Further a weighing machine is required to measure the output for each test as the nebulisers differ in output over time and between machines. Another disadvantage, as with

other wet aerosols, is that the person administering the challenge is also exposed to the aerosol as more than half of the amount generated by the nebuliser is expelled into the environment. Further the personnel are also exposed to saliva from the patient. There are also some difficulties encountered by the patient and these include the use of a nose peg, the production of a lot of saliva and the taste of salt. The time taken to perform the challenge with a wet aerosol in a mild asthmatic or healthy control maybe 70 minutes. This comprises preparation of solution and apparatus (about 10 minutes), actual challenge time which for mild asthmatics may be up to 30 minutes, and finally post challenge cleaning and sterilisation (about 30 minutes).

It is also known that wet aerosols of salt can be used for the purpose of increasing mucociliary clearance and inducing sputum in a subject. This technique has been used since the 1970's by physiotherapists to enhance the clearance of secretions from the airways of subjects having cystic fibrosis and bronchitis. In recent years the technique has been used with patients with HIV who are suspected of having *Pneumocystis carinii* which causes pneumonia and needs to be treated. Sputum analysis in patients suspected of having tuberculosis is also known as a simple technique to look for the disease.

By increasing the osmolarity of the airway surface liquid, water moves towards the lumen of the airway. This movement of water and the increased mucociliary clearance induced by hyperosmolarity also stimulates sputum production. The problem associated with this treatment is similar to the problem associated with the hyperosmolar saline challenge for the determination of airway narrowing. An expensive nebuliser is required to carry out the procedure.

**BRIEF DISCLOSURE OF THE INVENTION**

The present invention consists in a method for attempting to provoke airway narrowing in a subject comprising the steps of (a) causing the subject to inhale into the airways an effective amount of a substance capable of altering the osmolarity of airway surface liquid in the subject, which substance is in the form of a dispersible dry powder containing an effective proportion of particles of a respirable size, and (b) measuring in the subject a parameter indicative of the resistance to air flow of the subject's airways.

In another aspect the present invention consists in a method for inducing sputum comprising the step of causing a subject to inhale into his or her airways an effective amount of a substance capable of altering the osmolarity of airway surface liquid, the substance being in the form of a dispersible dry powder containing an effective proportion of particles of a respirable size.

In a still further aspect the present invention consists in a rupturable container containing an effective quantity of a substance capable of altering the osmolarity of airway surface liquid in a subject, the substance being in the form of a dispersible dry powder containing an effective proportion of particles of a respirable size.

The administration of a hyperosmolar challenge to a subject in the form of a dry powder rather than a wet aerosol enables the challenge to be administered through a conventional dry powder inhaler rather than through a nebuliser. This is highly advantageous as these inhalers are very cheap and are widely available. The time to perform a challenge is halved as there is no cleaning, sterilising, maintenance or weighing involved in the use of the dry powder test. It would also appear that smaller doses of challenge substance need to be administered in the dry state to achieve a desired

response than was required with that substance in the form of a wet aerosol.

As used in this specification, the term "airways" includes both the upper airways of the nose and the lower airways of the lungs. While the invention is particularly applicable in the latter case it is also applicable in the former case for the detection of actual or incipient rhinitis, which may be due to dry air or allergens, and similar conditions. While the invention is hereinafter described with particular reference to the lower airways, this teaching could be applied with equal effect to the airways of the nose.

The substance to be inhaled may be any substance that is biologically compatible with the subject and is capable of altering, normally increasing, the osmolarity of the airway surface liquid of the subject. Preferably the substance is a mineral salt or a sugar or sugar alcohol, more preferably it is selected from the group comprising salts of sodium or potassium, hexose and pentose sugars and their corresponding sugar alcohols. It is most preferred that the substance is selected from the group comprising sodium chloride, potassium chloride, mannitol and dextrose. Of the more preferred groups of substances sodium chloride and mannitol are the most preferred for their cheapness, their availability in the required particle size and their biological compatibility.

The substance is required to be inhaled into the airways, usually the first 8-12 generations, and an effective quantity is required to deposit on the surface of the airways. Preferably the substance will make contact with the airways surface in the first twelve generations of the airways. For this to happen it is necessary for the inhaled substance to be present initially in a sufficient quantity, for it to be sufficiently dispersible that it can be entrained by the subject's inhaled breath or by a propellant gas, and a sufficient proportion must be of a respirable particle size. The term "respirable particle size" is taken to mean a size that is sufficiently small that the particle will not settle out or impact against the subject's throat rather than be drawn out into the airways of the subject's lungs. In practice it has been found that particles of less than about seven microns are respirable.

In the case in which it is desired to induce airway narrowing, such as for testing for asthma, it may be desirable that as much of the powder is of a respirable size as is possible to reduce impaction on the oropharynx. In this case particles in the respirable range preferably comprise at least 10% of the substance by weight, more preferably at least 25%, even more preferably at least 40% and most preferably at least 50%. By contrast in the case where it is desired to induce sputum it may be desirable to include both respirable particles and non-respirable particles as the latter may induce coughing which will assist in the production of sputum. The desired dose in either case will depend upon individual circumstances and will be selected by the supervising health care personnel.

The method for attempting to provoke narrowing may be used for testing subjects for their susceptibility to asthma. In this case the subject may be administered a series of challenges each of a higher dose of the selected substance. After each challenge the subject will be tested for airway narrowing, usually by measuring the forced expiratory volume in 1 second (FEV<sub>1</sub>). Other known methods for measuring parameters indicative of airway narrowing could equally well be used and airway resistance is usually used for the nose. It will be appreciated that in many cases there will be no narrowing which is indicative of a negative propensity for asthma or rhinitis. In the case of subjects

susceptible to asthma there will be a narrowing of the airways proportional to the sensitivity of the subject to the effective administered dose of the substance, that is the dose actually reaching the airway surface. In each case the parameter indicative of resistance to airflow after challenge is compared with the same parameter measured before the challenge to indicate the presence or absence of airway narrowing.

The substance is preferably packaged in a rupturable hard capsule, e.g. gelatin. The capsules preferably contain doses of from 1 to 100 mg, preferably 5 to 40 mg in the case of challenge testing for asthma or rhinitis. In the case of sputum induction and mucociliary clearance, higher doses may prove desirable in subjects where airway narrowing is not a concern. In the case where it is desired to induce sputum from asthmatics or increase mucociliary clearance it may be necessary to premedicate the subject with a beta adrenoreceptor agonist, Intal or Nedocromil sodium before treatment to prevent the airways narrowing.

The present method for the induction of sputum may be used not only to collect sputum for analysis for the presence of viral or microbial pathogens but also in asthmatics to harvest inflammatory cells from the lung. This allows the state of activation of these inflammatory cells to be determined without invasive harvesting of the cells from the subject.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing the percentage of predicted FEV<sub>1</sub> for healthy and asthmatic subjects before and after a dry powder challenge according to the present invention;

FIG. 2 is a graph showing the dose of dry powder relative to the dose of wet aerosol required to cause an asthmatic response in susceptible subjects;

FIG. 3 is a graph showing nasal airflow resistance before and after a dry powder challenge according to the present invention; and

FIG. 4 is a graph showing nasal airflow resistance before and after two successive dry powder challenges according to the present invention.

#### BEST METHOD OF CARRYING OUT THE INVENTION AIM

To establish the efficacy of using a capsule system to deliver sodium chloride or mannitol particles for inducing airway narrowing in patients being treated for asthma.

#### SUBJECTS

Asthmatics born between Jun30, 1951 and Aug19, 1975 aged between 19-55 years were recruited from the local community. All were clinically recognised asthmatics and were being treated for this disease. All subjects were non-smokers, had a baseline forced expiratory volume in one second (FEV<sub>1</sub>) greater than 50% and a provocation dose of 4.5% saline to cause a 20% fall in FEV<sub>1</sub>(PD<sub>20</sub>)<30 ml.

The protocol for the 4.5% saline challenge was that described by Rodwell et al 1992, (American Review of Respiratory Disease, 1992; 146:1149-55). Subjects were excluded from the study if they had a chest infection in the previous six weeks. Subjects could not take bronchodilators for six hours before the lab visit, no corticosteroids were taken on the day of the study and no anti-histamines for three-five days before the study day.

This study was approved by the Royal Prince Alfred Hospital Ethics Committee and all subjects were required to

sign a consent form prior to commencing the study. The study was performed under the Clinical Trial Notification Scheme (CTN No 94-492,94-633) of the Therapeutics Goods Administration of the Commonwealth Department of Health of Australia.

## METHOD

### Experimental design

On the first visit to the laboratory each subject performed a standard hyperosmolar saline challenge with 4.5% saline delivered by an ultrasonic nebuliser. They were included in the study if they had a 20% reduction in FEV<sub>1</sub> provoked by this challenge. An asthmatic response is considered to be a reduction in FEV<sub>1</sub> greater than 15% from the pre-challenge value. They returned to the laboratory on 2 to 5 occasions. A minimum period of 48 hours separated each visit. On at least one of these occasions they inhaled an encapsulated dry powder of either sodium chloride or mannitol. Seventeen subjects performed the challenge with sodium chloride using a Halermatic (Fisons Pharmaceuticals) (Experiment 1), thirteen subjects performed a challenge with mannitol (Experiment 2) and 10 of these same subjects also performed a challenge with dry sodium chloride (Experiment 3) using a Ingelheim Inhalator (Boehringer Ingelheim).

### Preparation and device for delivering powder

Dry powder of sodium chloride or mannitol were prepared by spray drying an aqueous solution and milling, if necessary, so that particle size was in the respirable range (<7 microns). The powder was produced by Genentech Inc, South San Francisco, Calif. and sent in vials of 400 or 600 mg to our laboratory. There were two batches of sodium chloride and one of mannitol. Gravimetrically determined (change from known, known may be preferable) amounts (5, 10, 20 and 40 mg) of the dried powder were packaged in hard gelatin capsules (Gallipot, St Paul, Minn. 55120) by our laboratory staff. In order to reduce any possibility of re-hydration, this was carried out under controlled air conditions (temperature 16°–20°C, relative humidity 40%).

### Delivery of the powder to the subjects

Either the Halermatic or Ingelheim Inhalator was loaded with a capsule containing either 5, 10, 20, or 40 mg of sodium chloride or mannitol. The capsule was broken and the subject inhaled either once or twice to empty the capsule.

### Measurement of flow rates

The inspiratory flow rate through the Halermatic was measured indirectly by measuring the change in pressure at the mouth (Viggo-Spectrometer DTX Disposable Pressure Transducer, Oxnard, Calif., USA) during a maximal forced inspiration and values between 29–188 L/min were recorded (Miniwriter Type WTR771A, Watanabe Instruments Corp.). The low flow rates are due to the resistance of the device. For the Ingelheim Inhalator the inspiratory flow rate was measured by attaching it to a Minato Autospirometer (AS 800, Osaka, Japan) with the subject being asked to perform a maximum inspiratory manoeuvre through an empty Ingelheim Inhalator at the beginning of each study day. The Minato AS 800 was calibrated using a rotameter and variable flow.

### Measurement of the response

The FEV<sub>1</sub> was measured (Minato Autospirometer AS300, Minato Medical Science Co Ltd, Osaka, Japan) in duplicate, 60 seconds after the administration of the capsule.

The highest value was taken to calculate the airway response.

The reduction in FEV<sub>1</sub> for each dose was expressed as a percentage of the value for FEV<sub>1</sub> measured 60 seconds after an inhalation manoeuvre had been made from the inhaler containing an empty capsule.

The challenge was started by giving an empty capsule. The dose was started at 5 mg and was doubled with each exposure to a cumulative dose of 635 mg (5, 10, 20, 40, 2x40, 4x40, 4x40, 4x40 mg). This protocol for dosing was varied by repeating the same dose if the subject had a 'significant' reduction in FEV<sub>1</sub>.

The subjects performed spirometry for at least 30 minutes following the completion of each challenge to assess spontaneous recovery.

The airway response has been expressed in terms of the dose delivered that was required to provoke a 20% reduction in FEV<sub>1</sub> (PD<sub>20</sub>). A value for a 15% fall in FEV<sub>1</sub> could equally have been used (PD<sub>15</sub>). These values were obtained by linear interpolation from a graph relating % fall in FEV<sub>1</sub> to the dose of sodium chloride or mannitol delivered.

### Measurement of the particle size

The particle size was measured on a multistage liquid impinger (Astra Pharmaceuticals). This device measures particles in the range of 13–6.8 mm, 6.8–3.1 mm and <3.1 mm. This device was used to measure the dose of sodium chloride that was in the respirable range (<6.8 mm). To do this 25 ml of sodium chloride or mannitol of known osmolarity was placed in each of the 3 stages of the impinger.

Three 40 mg capsules of sodium chloride or mannitol were placed in either the Halermatic or an Inhalator and the powder was drawn, by a vacuum pump, through the impinger via a 'throat' at 60 L/min. The osmolarity of the fluid in the 3 stages was measured. The results of this showed that for the sodium chloride delivered by the Halermatic approximately 30% was within the respirable range. For the mannitol via the Ingelheim Inhalator it was 22% and for the sodium chloride via the Inhalator it was 16%.

### STATISTICS

The geometric mean and 95% confidence intervals have been calculated for the PD<sub>20</sub> for the wet aerosol challenge with 4.5% saline and the dry powder challenge with sodium chloride and mannitol. A paired t-test was carried out after log transformation of the values. Pre-challenge lung function (FEV<sub>1</sub>) was also compared using a paired t-test. The relationship between the PD<sub>20</sub> to dry mannitol and sodium chloride and wet 4.5% saline was determined using a Pearson's correlation coefficient. A value of p<0.05 was taken as significant.

Reference values  
For spirometry were taken from either Goldman & Becklake (*Am Rev Respir Dis* 1956;79:457–467) or for the studies with the Ingelheim Inhalator from Quanjer et al (*Eur Respir J* 1993; 6(Suppl 15):40). Reference values for normal responses to 4.5% saline are taken from Smith & Anderson (*Eur Respir J* 1990; 3:144–151). The upper limit of the fall in FEV<sub>1</sub> in healthy control subjects is 12%.

Asthmatic subjects

The results are presented in the three accompanying tables and illustrated in FIGS. 1 & 2 for all tests. The asthmatic medication currently being used by the subjects, the FEV<sub>1</sub> as a percentage of the predicted value on the initial visit (control day), the PD<sub>20</sub> values for the challenge with the wet

aerosol of 4.5% saline, the dry powder of mannitol or sodium chloride are given in Tables 1-3 for all subjects. For many subjects a second challenge was performed with the dry powder to demonstrate reproducibility of the airway response. For one study some of the subjects also performed a challenge test using methacholine and the PD<sub>20</sub> values for these subjects are also given in Table 2. There was no significant difference between the pre-challenge values for FEV<sub>1</sub> on each study day or the PD<sub>20</sub> provoked by the capsule on two test days for any of the experiments.

FIG. 1 illustrates, for each test, the pre and end challenge values for FEV<sub>1</sub> expressed as a percentage of the predicted normal value. This demonstrates clearly that the airway response to the dry powder challenge was different between

the healthy control subjects and the asthmatic subjects and that the airways of the asthmatic subjects narrowed in response to inhaling the dry powders (in all but one case). FIG. 2 illustrates the PD<sub>20</sub> to the dry powders of sodium chloride and mannitol in relation to the wet aerosol of 4.5% saline. This demonstrates that the subjects were somewhat more sensitive to the inhalation of the dry powders of sodium chloride and mannitol, compared with the wet aerosol of 4.5% saline delivered in a similar dose. This was particularly evident in Experiment 1 where there was a significantly lower dose of dry powder sodium chloride required to produce a 20% fall in FEV<sub>1</sub> compared with the wet aerosol ( $p < 0.02$ ).

TABLE 1

EXPERIMENT 1							
DRY POWDER SODIUM CHLORIDE VIA HALERMATIC							
Subject No.	Medications	Steroids		% Pred FEV <sub>1</sub>	4.5% Saline	NaCl#1	NaCl#2
		Dose (ug/day)	Duration (mth)	Pre chall Control Day	PD20 (mg)	PD20 (mg)	PD20 (mg)
1	Fenoterol			96.8	651.2	146	127
2	Salbutamol	BUD 800	3	94.2	149.4	161	96
3	Salbutamol			119.7	295.2	155	162
4	Salbutamol			88.1	249.8	121	118
5	Salbutamol			110.3	508.5	423	588
6	Salbutamol			75.7	232.7	126	105
7	Salbutamol			106.2	153.0	20.45	75.69
8	Salbutamol			103.3	166.5	106	52
9	Salbutamol			80.1	79.7	29	40
10	Terbutaline	BUD 1200	24	146.6	913.5	493.5	502.9
11	Salbutamol			86.4	725.4	36.1	79.5
12	Salbutamol	BEC 500	4	122.4	515.3	340.7	268.6
13	Terbutaline prn	BUD 800	6	81.5	205.7	257.99	128.8
14	Salbutamol	BEC 1000	48	66.2	58.5	87.93	132.03
15	Salbutamol	BUD 2000	23	76.3	16.7	19.4	62.9
16	Salbutamol			88.2	254.3	630	283.1
17	Salbutamol	BEC 400	48	79.6	137.7	52.6	19.16
		Mean		95.4	Geometric Mean	215.23	116.3
		SD		20.6	95% CI	[128.3,361.2]	[166.53,203.4]
					n = 17	n = 17	[74.6,183.1] n = 17
					p = 0.02	NS	
					n = 17	n = 17	

TABLE 2

EXPERIMENT 2							
□							
DRY POWDER MANNITOL VIA INGELHEIM INHALATOR							
Subj No.	Medications	Steroids		% Pred FEV <sub>1</sub>	4.5% Saline	Mannitol #1	Mannitol #2
		Dose (ug/day)	Duration (mth)	Pre chall Control day	PD20 (mg)	PD20 (mg)	PD20 (μmol)
1	Salbutamol			100	296.3	92	102
2	Salbutamol	BECL 400	72	102	32.85	61.7	43.1
3	Fenoterol	BECL 1000	69	65.7	7.2	20.5	53
4	Salbutamol	BUD 1600	24	65.5	163.35	131.2	183.2
5	Salbutamol	BECL 100	PRN	92.6	955.8	112.2	96.9
6	Salbutamol	BUD 2400	6	67.4	99.9	225	0.79
7	Salbutamol	BEC 800	8	61.2	38.7	11.6	6.2
8	Terbutaline	BUD 1200	36	129	916.65	366	463.1
9	Salbutamol	BUD 800	6	85.1	45.9	42.3	84.2
10	Salbutamol	BUD 800	24	87.1	378	295	337.1
11	Terb.Theo	BUD 6400	15	53.8	378	>635	1.77
12	Salbutamol			71.6	130.05	76	24.5
13	Salbutamol	BEC 500	PRN	116	229.95	77.5	

TABLE 2-continued

EXPERIMENT 2			□	DRY POWDER MANNITOL VIA INGELHEIM INHALATOR					
Subj No.	Medications	Dose (ug/day)	Duration (mth)	Steroids	% Pred FEV <sub>1</sub>	4.5% Saline	Mannitol #1	Mannitol #2	Mecholyl
				Pre chal Control day	PD20 (mg)	PD20 (mg)	PD20 (mg)	PD20 (mg)	PD20 (μmol)
14	Salbutamol			67.2	363.15	113.9			
		Mean	83.16	Geomean	149.4	85.84	77.99		
		SD	22.4	CI	[67.3,329.8]	[47.8,156.9]	[31.57,192.67]		
				n = 14	n = 13	n = 10			
					NS	NS			
					n = 13	n = 10			

TABLE 3

EXPERIMENT 3			DRY POWDER SODIUM CHLORIDE VIA INGELHEIM INHALATOR					
Subject No.	Medications	Steroids Dose (ug/day)	Duration (mth)	% Pred FEV <sub>1</sub> Pre chal Control Day	4.5% Saline PD20 (mg)	NaCl#1 PD20 (mg)	NaCl#2 PD20 (mg)	
1	Salbutamol			100	296.1	73.7	172.1	
2	Salbutamol	BECL 400	72	102	32.85	22.1	151	
3	Fenoterol	BECL 1000	60	65.7	7.2	50.1	18.2	
4	Salbutamol	BUD 1600	24	65.5	163.35	67.2	151	
5	Salbutamol	BECL 100	PRN	92.6	955.8	107.7	103.8	
6	Salbutamol	BUD 2400	6	67.4	99.9	168.2	138.22	
7	Terbutaline	BUD 1200	36	129	916.65	407.2		
8	Salbutamol	BUD 800	6	85.1	45.9	105.6	55.08	
9	Salbutamol	BUD 800	24	87.1	378	151.5	56.39	
10	Terb, Theo	BUD 6400	15	53.8	378	>635	>635	
		Mean	84.82	Geomean	152	95.3	86.67	
		SD	22.5	95% CI	[49.7,464.7]	[50.6,179.43]	[50.6,183.6]	
				n = 10	n = 9	n = 8		
					NS	NS		
					n = 9	n = 8		
		Mean		p = 0.096		p = 0.69		

40

## SPONTANEOUS RECOVERY

Experiment No 3 dry sodium chloride through Inhalator

The mean  $\pm$  SD value for FEV<sub>1</sub> expressed as a percentage of the pre-challenge pre-capsule value was 88.4%  $\pm$  10.6%, 30 minutes after challenge and 94.8%  $\pm$  7%, 60 mins after challenge.

## TIME &amp; NUMBER OF CAPSULES TAKEN for DRY CAPSULE CHALLENGE

For Experiment No 2

The mean time taken to perform the challenge with the dry capsule of mannitol was 10.0  $\pm$  3 min and varied from 6–14 minutes for the 13 subjects.

For Experiment No 3

The mean ( $\pm$  SD) time taken to perform the challenge with the dry capsule of sodium chloride was 10.6  $\pm$  3 min and varied from 6–15 minutes except in Subject 10 where it was 20 min. The mean number of capsules was 8.6  $\pm$  6.7 for subjects Nos 1–9. Subject 10 required 33 minutes but failed to respond. He was taking 6400 μg of Budesonide daily. Inspiratory Flow Rates through the Halermatic

The inspiratory flow rates in all but a few inhalations exceeded 50 L/min. The flows became lower as the dose of powder in the capsule increased. Thus when the empty capsule was in the Halermatic the median flow was 96 L/min and when the 40 mg capsules were inhaled it was 73 L/min. Inspiratory Flow Rates through the Inhalator

These were only measured once on each day of study. In all subjects the flow rate exceeded 43 L/min and the range was 43–70 L/min median value was 57 L/min.

## Oxygen Saturation during challenge

An Ohmeda Biox pulse oximeter (3700e Louisville, Colo. USA) was used to measure arterial oxygen saturation. This was performed as an index of safety to ensure that severe hypoxemia did not occur during the inhalation of mannitol. Only three subjects had a reduction in saturation of greater than 3% and all values for saturation remained within the normal range throughout the challenges with dry powders. Healthy Control Subjects

Five healthy control subjects (aged 19–22 yr) were studied, four received a dose of 620 mg and one 540 mg. None of these healthy volunteers, who acted as control subjects, recorded a PD<sub>20</sub> and the maximum % fall in FEV<sub>1</sub> was 6.5% with the range being 0–6.5%.

## DISCUSSION

The results of this study clearly demonstrate that both sodium chloride and mannitol, delivered from a capsule via either a Halermatic or Inhalator device, can provoke airway narrowing in the same asthmatic subjects who are sensitive to the wet aerosol preparation of saline. There was a good range in the severity of the hyperresponsiveness of asthma as demonstrated by the PD<sub>20</sub> to the wet aerosol. There were no adverse experiences requiring medical intervention. The mannitol powder was extremely well tolerated. Some subjects found difficulty in inhaling the powder of sodium chloride, particularly in the 40 mg dose. We estimated that less than 30% of the dose deposited in the lower respiratory

tract while the remainder impacted on the device and the throat. Ideally a greater percentage of the dose would have a particle size in the respirable range.

The advantages of the dry powder challenge over the wet aerosol challenge include; the faster time for challenge, the reduced necessity to clean apparatus and the potentially disposable nature of the inhalers.

This is the first ever report of the effect of inhalation of a dry powder of mannitol in human airways. This is the first report of the airway narrowing effects of dry particles of sodium chloride in known asthmatic subjects.

The only reference to inhalation of particles of sodium chloride in the respirable range is as a treatment for children suffering from bronchial asthma. Tikhomirov, Povolotska, & Zmievskaya (CC Number SU 1581325, Kind A Date 900730 Week 9113 (Basic) from the Soviet Union have reported that a course of 10–15 daily inhalations of a NaCl aerosol (containing 70–80% of 3 micron particles with a density of 9–12 mg/cubic meter) given in a chamber with air velocity of 0.1–0.2 m/sec, 40–60 vol % relative humidity at 16–18 degrees for periods gradually increasing from 6–15 min would increase remission of asthma of up to 1 year in 61.5% of cases. The concentration of dry powder particles in our application is much higher, being typically between 2.5–10 mg/liter (250–1620 mg/cubic meter), and the application for our study is acute airway narrowing for diagnostic purposes not treatment.

#### METHODS AND RESULTS FOR THE NASAL CHALLENGE

This study was performed on a single subject. The subject was familiar with the methods and could perform reproducible results. The subject voluntarily activated his alar nasal muscles to prevent nasal airway narrowing on inspiration, and breathed at normal tidal volume and rate with peak inspiratory flow of at least 0.5 L/sec. The studies were performed in a seated position in an air conditioned room with ambient temperature controlled between 21.5° and 23.5°C, and relative humidity between 55 and 65%.

Transnasal pressure and flow were measured by posterior rhinomanometry. Flow was measured using a modified Sullivan mask (Rescare, Australia) attached to a No.2 Fleish pneumotachograph. A firm air filled catheter was placed on the posterior tongue and sealed with the lips. This was referenced to the mask pressure and changes were measured with a Validyne MP45 pressure transducer (Validyne Corp, Northridge, Calif.). Pressure and flow signals were recorded at a rate of 12 Hertz and were plotted simultaneously on a computer screen.

The pressure/flow data from a sample of between 5 and 7 breaths was recorded. Rohrer's equation (pressure drop =  $k_1 \cdot \text{flow}^k \cdot \text{flow}_0^2$ ) was fitted to the data by least squares multiple linear regression. The nominal nasal resistance was then calculated from the fitted pressure drop at a flow rate of 0.5 L/sec in the inspiratory direction. Baseline nasal resistance was the average of at least 4 measurements. Once the baseline was established subjects underwent the challenge protocol and nasal resistance was measured at 1, 2, 4, 6, 8, 10, 15, and 20 minutes after the challenge.

The salt was delivered to the nasal mucosa using a Spinhaler device (Fisons Pharmaceuticals) loaded with half the total dose. The subject placed the loaded Spinhaler just inside one nostril and inhaled deeply. If the salt capsule was not empty after one inhalation, the subject performed another until the capsule was completely empty. The device was then reloaded and the other nostril was used.

The FIGS. 3 & 4 show nasal resistance over 4 baseline measurements before challenge, followed by measurements made after the challenge. Nasal resistance is expressed as cm H<sub>2</sub>O/sec. Both illustrate an increase in nasal resistance at 1 minute with a gradual fall to baseline over 15 minutes. This pattern is very similar to that seen with cold dry air both in terms of the degree of increase and the pattern of the subsequent fall to baseline. FIG. 4 shows results following inhalation of 40 mg, measurements for 20 minutes then a repeat dose of 40 mg.

Method for measuring mucociliary clearance Mucociliary clearance is assessed using a radioaerosol technique (99 mTc-sulphur colloid is commonly used). The radioaerosol should be generated with a nebuliser that produces droplets that have a mass median aerodynamic diameter (MMAD) of about 6 mm and a geometric standard deviation (GSD) under 2. A monodisperse aerosol would be ideal. The radioaerosol should be delivered with a controlled breathing pattern to achieve deposition in the large airways or the conducting airways. This is best achieved by having a target, on a computer or an oscilloscope screen, that sets the tidal volume and the inspiratory and expiratory times. Experimental data have shown that a tidal volume of 450 ml and a peak inspiratory flow rate of about 60 L/min is a good breathing pattern for central deposition. The activity delivered in the lungs should be about 40 MBq, so the delivery time should be adjusted accordingly. Usually 2 to 3 minutes is sufficient if the starting activity in the nebuliser is about 1 GBq.

Measurement of mucociliary clearance should start as soon as possible after the delivery of the radioaerosol. The best way to assess mucociliary clearance is using a gamma camera. Collection of emission images with a gamma camera gives good information about the initial deposition of radioaerosol in terms of distribution and intensity. Serial anterior/posterior images for about one hour provide the best data for assessing mucociliary clearance. A big advantage is that a regional analysis can be achieved for assessing mucociliary clearance of the large and small airways. Mucociliary clearance follows, usually, a bi-exponential pattern and curve fitting is commonly used to smooth the data. The salt or mannitol is administered after the collection of the first images that are used to assess the initial deposition of the radioaerosol.

#### CONCLUSION

Dry powders of substances that have the potential to increase the osmolarity of the airway surface liquid, when inhaled in an adequate dose containing an adequate amount of respirable particles are suitable for use in bronchial provocation testing to identify persons with airway hyperresponsiveness consistent with asthma. These same substances can also be inhaled into the nose to identify persons with rhinitis. These same substances have the potential to be used to induce sputum and increase mucociliary clearance.

I claim:

1. A method for attempting to provoke airway narrowing in a subject comprising the steps of (a) causing the subject to inhale into subject's airways an effective amount of a substance capable of increasing the osmolarity of airway surface liquid in the subject, which substance is in the form of a dry dispersible powder, other than a dry powder dissolved in a liquid, containing an effective proportion of particles of a respirable size, and (b) measuring in the subject a parameter indicative of the resistance to air flow of the subject's airway.
2. A method as claimed in claim 1 in which the subject is caused to inhale the substance into the airways of a lung.

**13**

**3.** A method as claimed in claim **1** in which the subject is caused to inhale the substance into a nasal airway.

**4.** A method as claimed in claim **1** in which the substance is selected from the group comprising mineral salts, sugars and sugar alcohols.

**5.** A method as claimed in claim **4** in which the substance is selected from the group comprising salts of sodium or potassium, hexose and pentose sugars and their corresponding sugar alcohols.

**6.** A method as claimed in claim **5** in which the substance is selected from the group comprising sodium chloride, potassium chloride, mannitol and dextrose.

**7.** A method as claimed in claim **1** in which an effective quantity of the dry particles have a maximum dimension of seven microns.

**8.** A method as claimed in claim **1** in which the proportion of the particles having a respirable size is at least 10% by weight of the substance, preferably at least 25%, more preferably at least 40% and most preferably at least 50%.

**9.** A method as claimed in claim **1** in which the parameter indicative of airway narrowing that is measured comprises measuring a reduction in forced expiratory volume in one second.

**10.** A method as claimed in claim **1** in which the substance is packaged in a rupturable hard capsule.

**11.** A method as claimed in claim **10** in which the capsule contains from 1 to 100 mg of the substance, preferably 5 to 40 mg.

**12.** A method for increasing mucociliary clearance or inducing sputum comprising the step of causing a subject to inhale into the subject's airways an effective amount of a substance capable of increasing the osmolarity of airway surface liquid, the substance being in the form of a dispers-

**14**

ible dry powder, other than a dry powder dissolved in a liquid, containing an effective proportion of particles of a respirable size.

**13.** A method as claimed in claim **12** in which the subject is caused to inhale the substance into the airways of a lung.

**14.** A method as claimed in claim **12** in which the subject is caused to inhale the substance into a nasal airway.

**15.** A method as claimed in claim **12** in which the substance is selected from the group comprising mineral salts, sugars and sugar alcohols.

**16.** A method as claimed in claim **15** in which the substance is selected from the group comprising salts of sodium or potassium, hexose and pentose sugars and their corresponding sugar alcohols.

**17.** A method as claimed in claim **16** in which the substance is selected from the group comprising sodium chloride, potassium chloride, mannitol and dextrose.

**18.** A method as claimed in claim **12** in which an effective quantity of the dry particles have a maximum dimension of seven microns.

**19.** A method as claimed in claim **12** in which the proportion of the particles having a respirable size is at least 10% by weight of the substance, preferably at least 25%, more preferably at least 40% and most preferably at least 50%.

**20.** A method as claimed in claim **12** in which the substance is packaged in a rupturable hard capsule.

**21.** A method as claimed in claim **20** in which the capsule contains from 1 to 100 mg of the substance, preferably 5 to 40 mg.

\* \* \* \*

# Exhibit H

Brd.  
o/y.

ROCKEY, MILNAMOW & KATZ, LTD.  
TWO PRUDENTIAL PLAZA  
180 N. STETSON AVENUE, SUITE 4700  
CHICAGO, ILLINOIS 60601  
(312) 616-5400

**FAX TRANSMITTAL SHEET**

**FAX NO. (312) 616-5460**

To: Mr. Chris O'Sullivan  
F.B. Rice & Co.

Fax: 011-612-9810 8200

Date: February 25, 1999

From: Dr. Elaine M. Ramesh

Re: U.S. Patent No. 5,817,028  
Your Reference No. 72184  
Our Reference No. FBR2173P0010US



Number of Pages: 4 (Including This Transmittal Sheet)

**SPECIAL INSTRUCTIONS FOR THE RECEIVING PARTY ONLY:**

Mr. O'Sullivan:

Please find enclosed a copy of a Certificate of Correction and accompanying transmittal letter which were filed in the U.S. Patent and Trademark Office on February 23, 1999.

One of our Washington associates spoke with the supervisory Examiner responsible for the application about the corrections on February 22, 1999. The Examiner indicated that such changes should be approved when formally submitted.

Our associate has also informed us that the processing time for the Certificate will be at least four months, so I will contact you again in approximately five months to let you know whether the Certificate was approved. Please call me if you have further questions regarding this matter.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Sandra Anderson	)	Attorney Docket No.
		)	FBR2173P0010US
Patent No.:	5,817,028	)	
		)	
Filed:	October 6, 1998	)	Examiner: S. Huang
		)	
For:	Method and Device for the	)	
	Provocation of Air Passage	)	
	Narrowing and/or The Induction	)	
	of Sputum	)	
		)	

REQUEST FOR CERTIFICATE OF CORRECTION

Assistant Commissioner For Patents  
Washington, D.C. 20231

Sir:

United States Letters Patent No. 5,817,028 was granted to Sandra D. Anderson on the basis of the above application, and is assigned to Central Sydney Area Health Service. Printing errors were made as summarized on the enclosed Form No. PTO-1050, submitted herewith in duplicate.

The correction to the Abstract is necessitated by the Applicant's typographical error of substituting a "u" for an "i". As the correct spelling can be found throughout the patent (for example in col. 3, line 67) this correction adds does not constitute new matter.

The corrections to column 6 and 12 are necessitated by the Applicant's typographical error of substituting an "m" for a " $\mu$ ". The unit  $\mu$ m stands for microns. As the respirable particle size has been defined in the patent in terms of microns, (for example in col. 3, line 39 and col. 5, line 30) this correction does not constitute new matter.

The correction to col. 11 is necessitated by a Patent and Trademark Office mistake, as the correct form of the equation can be found on page 19, line 5 of the specification as originally filed.

It is requested that a Certificate of Correction be issued embodying the enclosed corrections.

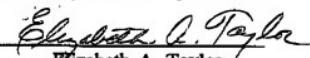
Respectfully submitted,

By   
Lisa V. Mueller, Reg. No. 38,978

Rockey, Milnamow & Katz, Ltd.  
180 North Stetson, Suite 4700  
Chicago, Illinois 60601  
(312) 616-5400

CERTIFICATE OF MAILING

I hereby certify that this Paper, Certificate of Correction Request (in duplicate), and check are being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, this 23rd day of February, 1999.

  
Elizabeth A. Taylor

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.  
(Also Form PTO-1050).

UNITED STATES PATENT AND TRADEMARK OFFICE  
CERTIFICATE OF CORRECTION

PATENT NO.: 5,814,028

DATED : October 6, 1998

INVENTOR(S): Sandra Doreen Anderson

It is hereby certified that error appear(s) in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Abstract , line 28; please delete "rhinitus" and insert --rhinitis--

Col. 6, line 28; please delete "13-6.8 mm, 6.8-3.1 mm" and insert --13-6.8  $\mu\text{m}$ , 6.8-3.1  $\mu\text{m}$ --

Col. 6, line 29; please delete "mm" and insert -- $\mu\text{m}$ --

Col. 11, line 53; please delete " $k_1$  \*flow +  $k_2$  \*flow<sub>2</sub>" and insert -- $k_1$  \*flow +  $k_2$  \*flow<sup>2</sup>--

Col. 12, line 16; please delete "mm" and insert -- $\mu\text{m}$ --

## MAILING ADDRESS OF SENDER:

ROCKY, MILNAMOW & KATZ, LTD.  
180 North Stetson Avenue, Suite 4700  
Chicago, Illinois 60601  
(312) 616-5400

PATENT NO. 5,817,028

No. of additional copies: 1

# Exhibit I



# UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents  
United States Patent and Trademark Office  
P.O. Box 1450  
Alexandria, VA 22313-1450  
[www.uspto.gov](http://www.uspto.gov)

Customer No 000000

ISTMT

DATE PRINTED  
11/23/2010

ALLEN J HOOVER  
DRESSLER GOLDSMITH MILNAMOW & KATZ LTD  
TWO PRUDENTIAL PLAZA STE 4700  
180 N STETSON AVENUE

## MAINTENANCE FEE STATEMENT

According to the records of the U.S. Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,817,028	\$880.00	\$0.00	03/21/02	08/696,987	10/06/98	11/04/96	04	NO	FRFBR2173P00

# Exhibit J



# UNITED STATES PATENT AND TRADEMARK OFFICE

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TWO PRUDENTIAL PLAZA STE 4700  
180 N STETSON AVENUE

## MAINTENANCE FEE STATEMENT

According to the records of the U.S. Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,817,028	\$2,300.00	\$0.00	03/13/06	08/696,987	10/06/98	11/04/96	08	NO	FRFBR2173P00

# Exhibit K



# UNITED STATES PATENT AND TRADEMARK OFFICE

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11/23/2010

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DRESSLER GOLDSMITH MILNAMOW & KATZ LTD  
TWO PRUDENTIAL PLAZA STE 4700  
180 N STETSON AVENUE

## MAINTENANCE FEE STATEMENT

According to the records of the U.S. Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,817,028	\$4,110.00	\$0.00	03/31/10	08/696,987	10/06/98	11/04/96	12	NO	ANDERSON,SAN DRA DOREEN

# Exhibit L



PIEDMONT CONSULTING GROUP, LLC

1840 GATEWAY DRIVE, SUITE 200  
SAN MATEO, CA 94404  
PHONE: 650.378.1275  
FAX: 650.523.8557  
[WWW.PCGMEDICAL.COM](http://WWW.PCGMEDICAL.COM)

November 19, 2003 4 *L.G.*

Badrul Chowdhury, M.D., Division Director  
U.S. Food and Drug Administration  
Division of Pulmonary and Allergy Drug Products  
5600 Fishers Lane  
Rockville, MD 20857-0001

**Re: IND #70,277; S-000 for ARIDOL™, Mannitol Powder for Inhalation**

**Sponsor: Pharmaxis Ltd., 10 Rodborough Rd, Frenchs Forest, NSW 2086,  
Australia**

Dear Dr. Chowdhury:

Enclosed are three copies of an initial IND submission for Aridol™, mannitol powder for inhalation, which is being developed as a bronchoprovocation agent.

A pre-IND meeting was held on July 19, 2004 between representatives for Pharmaxis Ltd. and representatives for the Division of Pulmonary and Allergy Drug Products. The minutes of that meeting and our response to the minutes are included in Section 10 of this filing for convenience.

One of the topics of discussion at the meeting was the design of a Phase 3 study. A protocol for the study is included in Section 6.a of this submission. It would be appreciated if your staff could review the protocol for acceptability as a pivotal Phase 3 study. We would be able to participate in a teleconference or attend a meeting to discuss the results of the review.

At the time of the pre-IND meeting, a pre-IND number, 70,277, was assigned to the project. It is my understanding that this number will be the number for the IND, and it has been incorporated into the documents.

Please contact me if there are any questions or a meeting or teleconference is needed.

Sincerely yours,

*Martha R Charney*  
Martha R. Charney, Ph.D.  
Vice President, Piedmont Consulting Group, LLC.

Copy: B. Charlton, M.D., Pharmaxis Ltd.  
R. Sinani, B.S., Pharmaxis Ltd.

# Exhibit M



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 70,277

Pharmaxis Ltd.  
c/o Piedmont Consulting Group, LLC  
1840 Gateway Drive, Suite 200  
San Mateo, CA 94404

Attention:      Martha R. Charney, Ph. D.  
                  Vice President, Piedmont Consulting Group, LLC

Dear Dr. Charney:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned:      70,277

Sponsor:      Pharmaxis Ltd.

Name of Drug:      Aridol (mannitol) powder for inhalation

Date of Submission:      November 19, 2004

Date of Receipt:      November 22, 2004

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before December 22, 2004, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations).

Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (<http://clinicaltrials.gov> & <http://prsinfo.clinicaltrials.gov>). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site <http://prsinfo.clinicaltrials.gov>.

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to the following address:

U.S. Postal Service/Courier/Overnight Mail:  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Pulmonary and Allergy Drug Products, HFD-570  
Attention: Division Document Room, 8B-45  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, call Christine Yu, R.Ph., Regulatory Project Manager, at 301-827-1051.

Sincerely,

*(See appended electronic signature page)*

Sandy Barnes  
Supervisory CSO  
Division of Pulmonary and Allergy Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Christine Yu  
12/2/04 05:33:06 PM  
Signing for Sandy Barnes, CPMS

# Exhibit N

**SUBMISSION OF ORIGINAL NDA 22-368 for ARIDOL<sup>TM</sup>  
(mannitol bronchial challenge test)**

February 27, 2009

Badrul Chowdhury, MD, PhD, Division Director  
Division of Pulmonary and Allergy Drug Products  
ODEII/OND/FDA  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Dear Dr. Chowdhury:

In accordance with 21 CFR 314.50, Pharmaxis Ltd is submitting the enclosed original New Drug Application (NDA) for Aridol (mannitol bronchial challenge test [BCT]), indicated for "*the assessment of bronchial hyperresponsiveness to aid in the diagnosis of patients ≥ 6 years of age with symptoms of or suggestive of asthma.*" Previous information concerning this product has been submitted to the Agency under IND 70,277.

**Electronic Submission**

This NDA is structured according to the ICH eCTD Specification V 3.2.2, July 16, 2008, and is being submitted entirely electronically using the Electronic Submission Gateway (ESG) provided by our contract publisher, Apyx, Inc. The size of this submission is approximately 1.6 GB. All files were checked and verified to be free of viruses using Computer Associates eTrust Antivirus, program 7.1.501, and engine version 31.6.6369, with a release date of February 23, 2009, or later.

**User Fees Waiver**

Under the small business waiver provision, Section 736(d)(1)(D)<sup>1</sup> of the Federal Food, Drug, and Cosmetic Act, the human drug application fee *Waiver Request 2008.063* for NDA 22-368 for Aridol (mannitol BCT) was granted on August 29, 2008. A copy of the letter is provided in Module 1 of this NDA.

**Proprietary Name Review**

The trade name "Aridol" was submitted to the Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Drug Marketing, Advertising, and Communications (DDMAC) for review on October 1, 2008 (IND 70,277; S-0061). Under the new PDUFA proprietary name review guideline, the PDUFA date for submission of the proprietary name is March 30, 2009.

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<sup>1</sup> 21 U.S.C. 379h(d)(1)(D)

We trust that we have included all the necessary administrative information and technical data in this NDA/eCTD. We thank you for your valuable advice throughout the Aridol development program and are particularly grateful to Ms. Miranda Raggio for her prompt assistance during the preparation of this NDA. We look forward to working closely with the Division to expedite this NDA review. If you have any questions concerning this original NDA submission or need additional information, please contact Valerie Waltman by telephone at (610) 336-5120 ext 103, by FAX at (610) 363-5926, or by e-mail at [valerie.waltman@pharmaxis.com](mailto:valerie.waltman@pharmaxis.com).

Sincerely,



Pauliana Hall, RAC (US, EU, and Canada)  
US Agent and Regulatory Consultant for Pharmaxis Ltd.

cc: Ms. Miranda Raggio, RN, BSN, MA, Regulatory Health Program Manager (e-mail)

# Exhibit O



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-368

**NDA ACKNOWLEDGMENT**

Pharmaxis, Inc.  
403 Gordon Drive  
Exton, PA 19341

Attention: Valerie Waltman, MS  
Senior Manager, Regulatory Affairs

Dear Ms. Waltman:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Aridol (mannitol dry powder capsules)

Date of Application: February 26, 2009

Date of Receipt: February 27, 2009

Our Reference Number: NDA 22-368

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 28, 2009, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Pulmonary and Allergy Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me, Regulatory Project Manager, at (301) 796-2109.

Sincerely,

*Miranda Raggio, Senior Regulatory Project Manager*

Miranda Raggio  
Senior Regulatory Project Manager  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Office of New Drugs  
Center for Drug Evaluation and Research

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/s/  
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Miranda Raggio  
3/6/2009 12:44:10 PM

# Exhibit P



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration  
Silver Spring MD 20993

NDA 22368

**COMPLETE RESPONSE**

Pharmaxis, Inc.  
403 Gordon Drive  
Exton, PA 19341

Attention: Valerie Waltman, MS  
Senior Manager, Regulatory Affairs

Dear Ms. Waltman:

Please refer to your new drug application (NDA) dated February 26, 2009, received February 27, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aridol (mannitol inhalation powder).

We acknowledge receipt of your amendments dated June 11, July 17, August 31, September 4 and 8, October 15, 22, and 30, November 3 and 13, December 4, 15, 17, 18, 21, 22, and 23, 2009.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

If you have any questions, call Miranda Raggio, Regulatory Project Manager, at (301) 796-2109.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Division Director  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Office of New Drugs  
Center for Drug Evaluation and Research

Enclosure:Labeling 12-23-09

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22368	ORIG-1	PHARMAXIS LTD	ARIDOL POWDER FOR INHALATION

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/s/

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BADRUL A CHOWDHURY  
12/23/2009

# Exhibit Q



## NDA 22-368 COMPLETE RESPONSE RESUBMISSION

April 7, 2010

Badrul Chowdhury, M.D., Ph.D., Division Director  
Division of Pulmonary and Allergy Drug Products  
ODEII/OND/FDA  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA No./Product:** NDA 22-368 Aridol™ (mannitol inhalation powder)  
**NDA Amendment:** Complete Response Resubmission  
**Sequence No.:** 0020

Dear Dr. Chowdhury:

Reference is made to the original New Drug Application (NDA) 22-368 for Aridol™ (mannitol inhalation powder) submitted on February 27, 2009, and FDA's Complete Response Letter (CRL) dated December 23, 2009, indicating that the NDA for Aridol cannot be approved in its present form.

The purpose of this amendment is to provide a Complete Response Resubmission addressing the remaining NDA final approval issues. The enclosed Complete Response Resubmission (Sequence No. 0020) contains the following sections:



The size of this submission is approximately 20 MB. All files were checked and verified to be free of viruses using ESET NOD32 Antivirus, version of virus signature database 5002, updated on 04/05/2010 or later.

If you have any questions concerning this Complete Response Resubmission, please contact me at (610) 363-5120 ext. 103, FAX (610) 363-5926, or e-mail valerie.waltman@pharmaxis.com.

Sincerely,

A handwritten signature in cursive ink that reads "Valerie Waltman".

Valerie Waltman, MS  
Senior Manager, Regulatory Affairs

cc: Miranda Raggio, Regulatory Project Manager (cover letter only)  
Alicia Mozzachio, Office of Compliance (cover letter only)

# Exhibit R



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-368

Pharmaxis, Inc.  
403 Gordon Drive  
Exton, PA 19341

Attention: Valerie Waltman, MS  
Senior Manager, Regulatory Affairs

Dear Ms. Waltman:

Please refer to your new drug application (NDA) dated February 27, 2009, received February 27, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Aridol.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 27, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 30, 2009.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We have the following requests for information:

Chemistry, Manufacturing, and Controls

1. Provide qualification data for the impurity Sorbitol in your drug substance as per ICH Q3A document. Reference to a compendial limit is not considered sufficient evidence of safety.
2. Provide safety qualification of drug degradation products according to the ICH Guidance Q3B.
3. Provide safety qualification of any extractable/leachables from the device.
4. The capsule sizes for the proposed RS01 Model 7 device are similar to the capsule sizes of other commercial marketed inhalation products. Provide available in vitro performance data for your mannitol capsules being delivered in other devices (Handihaler, Aerolizer, etc.) and for other commercial capsules being delivered by you device to see if interchanging the devices and capsules provides comparable in vitro performance results.
5. Provide dose proportionality results for APSD and DDU of the drug product for all the proposed doses using the proposed analytical methods.
6. Revise the proposed DDU specifications to be reflective of the proposal in the Draft MDI/DPI guidance. Refer to the comments sent in the communication dated May 29, 2008, on DDU methods provided at the pre-NDA meeting with reference to using the 0 mg capsule. Regarding the test method for measuring Delivered Dose of Mannitol from Capsules (TM032), clarify the differences between the DDU measured in Capsule set # 7, Capsule set #8, and Capsule set # 9 since all three use 4 x 40 mg capsules.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

If you have any questions, call Miranda Raggio, Senior Regulatory Project Manager, at (301) 796-2109.

Sincerely,

*[See appended electronic signature page]*

Badrul A. Chowdhury, M.D, Ph.D.  
Director  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Office of New Drugs  
Center for Drug Evaluation and Research

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/s/  
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Badrul Chowdhury  
5/12/2009 02:49:01 PM

# Exhibit S

**FDA Correspondence Log for IND number 70,277 and NDA number 022368**

Date	Reference	Subject
June 18, 2004	N/A	Pre-IND Briefing package
July 19, 2004	Meeting	Pre-IND Meeting held on 7/19/04
November 19, 2004	IND 70,277-0000	Original IND (Study DPM-A-305)
January 31, 2006	IND 70,277-0011	Annual Report
February 22, 2007	IND 70,277-0030	Annual Report (including Final CSR DPM-A-301 & DPM-B-201/202 (no appendices))
May 30, 2007	IND 70,277-0033	Response to FDA Comments
January 7, 2008	IND 70,277-0043	Update of Aridol CMC CTD Format
March 12, 2008	Meeting	pre-NDA Meeting Clinical/Non-Clinical
March 13, 2008	Meeting	Pre-NDA Meeting CMC
May 20, 2008	IND 70,277-0053	IND Annual Report
September 1, 2008	IND 70,277-0061	Trade name request: Aridol
February 27, 2009	NDA 22-368-0000	Original NDA
August 31, 2009	NDA 22-368-0003	120-day safety update report
October 22, 2009	NDA 22-368-0007	Meeting background information for PADAC 11/20/09
April 7, 2010	NDA 22-368-0020	Complete Response Resubmission
October 5, 2010	NDA 22-368	Aridol NDA 22-368 APPROVAL LETTER